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Synthesis of Novel Alkaloids Using Squaric Acid Esters

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Dissertation submitted to the Eberly College of Arts and Sciences at West Virginia University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in
Organic Chemistry

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Abstract
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Peter S. Zehr

A novel route to cyclopenta[b]quinoline-1-ones and –ols has been developed. Substituted cyclopenta[b]quinolin-1-ones were prepared by thermal ring-expansion of substituted N-BOC protected 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones forming the corresponding 2-aminophenylmethylidene substituted 4-cyclopentene-1,3-diones. Deprotection of the amine resulted in spontaneous condensation to give cyclopenta[b]quinolin-1-ones. Sodium borohydride reduction of these products produced cyclopenta[b]quinolin-1-ols. The key step in the sequence is a thermally induced ring-expansion of 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones. Changing the amino protecting group had no effect on the ring size selectivity of the thermal ring expansion. The thermal ring expansion of the corresponding nitro derivative suggests that electron withdrawing substituents may alter the selectivity of the ring formation. The attempted base mediated, copper mediated, copper catalyzed and palladium catalyzed indolization reaction were not further examined since the desired products were not obtained. The N-iodosuccinimide, N-chlorosuccinimide mediated and palladium catalyzed ring expansion reactions were also not further examined. The copper acetate catalyzed indolization of the N-acetyl derivative may lead to the preparation of novel 2-substituted indoles. In the Cul mediated reactions with N-benzyl the project was dropped since the starting material was difficult to synthesize. A novel route to indoloquinones has been developed. This methodology may lead to the synthesis of a natural product, as well as several novel indoloquinones.
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Table of Contents

Title page .............................................................................................................................. i
Abstract................................................................................................................................ii
Acknowledgments........................................................................................................... iii
Table of Contents.............................................................................................................. iv
List of Figures ..................................................................................................................... vii
List of Schemes .................................................................................................................. xv
List of Tables ..................................................................................................................... xvii

Part I

A Novel Entry to Cyclopenta[b]quinolines via Thermal Ring-Expansion of (2-Aminophenyl)-Ethynyl-Substituted
Cyclobutenone Derivatives

1. Introduction ..................................................................................................................... 1
   a. 1.1. Quinoline Syntheses: Intramolecular Cyclization of Anilines ................. 2
   b. 1.2. Quinoline Syntheses: Cyclization of Ortho-Disubstituted Benzenes .............................................................................................................. 5
   c. 1.3. Modern Quinoline Syntheses .................................................................. 7
   d. 1.4. Cyclobutenediones ................................................................................... 8
2. Results and Discussion ................................................................................................. 11
   a. 2.1. N-BOC Protected Derivatives ............................................................... 12
   b. 2.2. N-Acetyl and N-benzyl aniline ............................................................. 27
Part II

Attempted Indolizations and Additional Ring Expansions

1. Introduction ..................................................................................................... 34
   a. 1.1. Indolization Methods ..................................................................... 35
   b. 1.2. Electrophilic Ring Expansions 4-Hydroxy-2-cyclobuten-1-ones .... 38

2. Results and Discussion...................................................................................40
   a. 2.1. Base Mediated Indole Formation .................................................. 41
   b. 2.2. Attempted Copper Mediated Indole Formation .............................. 42
   c. 2.3. Copper Acetate Catalyzed Indole Formation ................................. 44
   d. 2.4. Attempted Palladium Catalyzed Indole Formation or Ring
           Expansions............................................................................................... 45
   e. 2.5. N-Iodosuccinimide Mediated Ring Expansion ..................... 45
   f. 2.6. N-Chlorosuccinimide Mediated Ring Expansion ...................... 46

3. Conclusions .................................................................................................... 48
Part III

Synthesis of Novel Indoloquinones

1. Introduction ....................................................................................................49
2. Results and Discussion .................................................................................52
3. Conclusions ....................................................................................................58

Part IV

Experimental Section

1. General Procedures .......................................................................................59
2. Experimental Details ......................................................................................60
3. References .....................................................................................................97
4. Appendix ......................................................................................................102
List of Figures

Figure 1: Biologically Active Quinoline .................................................................1

Figure 2: Gradient Heteronuclear Multiple Quantum Coherence Spectrum of 35 .................................................................16

Figure 3: Gradient Heteronuclear Multiple Bond Coherence Spectrum of 35 ................................................................................17

Figure 3A: Indoloquinone Containing Natural Products ..................................49

Figure 4: $^1$H Spectrum of (4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester 37b ..............................................................103

Figure 5: $^{13}$C Spectrum of (4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester 37b .................................................................104

Figure 6: $^1$H Spectrum of (2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester 37c ..............................................................105

Figure 7: $^{13}$C Spectrum of (2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester 37c .................................................................106

Figure 8: $^1$H Spectrum of (2-Iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 37d ..............................................................107

Figure 9: $^{13}$C Spectrum of (2-Iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 37d .................................................................108

Figure 10: $^1$H Spectrum of (4-Chloro-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester 38b ..............................................................109

Figure 11: $^{13}$C Spectrum of (4-Chloro-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester 38b ..............................................................110

Figure 12: $^1$H Spectrum of (5-Methoxy-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester 38c ..............................................................111

Figure 13: $^{13}$C Spectrum of (5-Methoxy-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester 38c ..............................................................112

Figure 14: $^1$H Spectrum of (5-Methyl-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester 38d ..............................................................113
Figure 15: $^{13}$C Spectrum of (5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 38d ......................................................................................................................... 114

Figure 16: $^1$H Spectrum of (4-trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 38e ......................................................................................................................... 115

Figure 17: $^{13}$C Spectrum of (4-trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 38e ......................................................................................................................... 116

Figure 18: $^1$H Spectrum of (4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 26b ......................................................................................................................... 117

Figure 19: $^{13}$C Spectrum of (4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 26b ......................................................................................................................... 118

Figure 20: $^1$H Spectrum of (2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester 26c ......................................................................................................................... 119

Figure 21: $^{13}$C Spectrum of (2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester 26c ......................................................................................................................... 120

Figure 22: $^1$H Spectrum of (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 26d ......................................................................................................................... 121

Figure 23: $^{13}$C Spectrum of (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 26d ......................................................................................................................... 122

Figure 24: $^1$H Spectrum of (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 26e ......................................................................................................................... 123

Figure 25: $^{13}$C Spectrum of (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 26e ......................................................................................................................... 124

Figure 26: $^1$H Spectrum of [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28a ............................................................................................................... 125

Figure 27: $^{13}$C Spectrum of [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28a ............................................................................................................... 126

Figure 28: $^1$H Spectrum of [4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28b ............................................................................................................... 127

Figure 29: $^{13}$C Spectrum of [4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28b ............................................................................................................... 128
Figure 30: $^1$H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester $28c$ and butyl addition product of diisopropyl squarate .......................................................... 129

Figure 31: $^{13}$C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester $28c$ and butyl addition product of diisopropyl squarate .......................................................... 130

Figure 32: $^1$H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester $28c$ .... 131

Figure 33: $^{13}$C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester $28c$ .... 132

Figure 34: $^1$H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester $28d$ .... 133

Figure 35: $^{13}$C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester $28d$ .... 134

Figure 36: $^1$H Spectrum of [4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester $28e$ ............ 135

Figure 37: $^{13}$C Spectrum of [4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester $28e$ ............ 136

Figure 38: $^1$H Spectrum of [2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester $33a$ ...................... 137

Figure 39: $^{13}$C Spectrum of [2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester $33a$ ...................... 138

Figure 40: $^1$H Spectrum of [4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester $33b$ ...... 139

Figure 41: $^{13}$C Spectrum of [4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester $33b$ ...... 140

Figure 42: $^1$H Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxy-phenyl]-carbamic acid 1,1-dimethylethyl ester $33c$ .... 141

Figure 43: $^{13}$C Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxy-phenyl]-carbamic acid 1,1-dimethylethyl ester $33c$ .... 142
Figure 44: $^1$H Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester 33d

Figure 45: $^{13}$C Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester 33d

Figure 46: $^1$H Spectrum of [4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyranylidene]-carbamic acid 1,1-dimethylethyl ester 33e

Figure 47: $^{13}$C Spectrum of [4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyranylidene]-carbamic acid 1,1-dimethylethyl ester 33e

Figure 48: $^1$H Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-one 34a

Figure 49: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-one 34a

Figure 50: $^1$H Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-one 34b

Figure 51: $^{13}$C Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-one 34b

Figure 52: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-one 34c

Figure 53: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-one 34c

Figure 54: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-one 34d

Figure 55: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-one 34d

Figure 56: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-aza-cyclopenta[b]quinolin-1-one 34e

Figure 57: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-aza-cyclopenta[b]quinolin-1-one 34e

Figure 58: $^1$H Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35a
Figure 59: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35a

Figure 60: $^1$H Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35b

Figure 61: $^{13}$C Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35b

Figure 62: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-ol 35c

Figure 63: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-ol 35c

Figure 64: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-ol 35d

Figure 65: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-ol 35d

Figure 66: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-azacyclopenta[b]quinolin-1-ol 35e

Figure 67: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-azacyclopenta[b]quinolin-1-ol 35e

Figure 68: $^1$H Spectrum of [2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethyl ester 41

Figure 69: $^{13}$C Spectrum of [2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethyl ester 41

Figure 70: $^1$H Spectrum of E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethyl ester 42

Figure 71: $^{13}$C Spectrum of E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethyl ester 42

Figure 72: $^1$H Spectrum of 2-(1-Methylethoxy)-3-methylcyclopenta[b]quinolin-1-one 43

Figure 73: $^{13}$C Spectrum of 2-(1-Methylethoxy)-3-methylcyclopenta[b]quinolin-1-one 43
Figure 74: $^1$H Spectrum of 2-(1-methylethoxy)-3-methylcyclopenta[b]quinolin-1-ol 44 .................................................................................................................... 173

Figure 75: $^{13}$C Spectrum of 2-(1-methylethoxy)-3-methylcyclopenta[b]quinolin-1-ol 44 .................................................................................................................... 174

Figure 76: $^1$H Spectrum of N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide 46 ............................................................................................................. 175

Figure 77: $^{13}$C Spectrum of N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide 46 ............................................................................................................. 176

Figure 78: $^1$H Spectrum of N-[2-(3,4-Diisopropoxy-2,5-dioxo-cyclopent-3-enylenemethyl)-phenyl]-acetamide 51 ............................................................................................................. 177

Figure 79: $^{13}$C Spectrum of N-[2-(3,4-Diisopropoxy-2,5-dioxo-cyclopent-3-enylenemethyl)-phenyl]-acetamide 51 ............................................................................................................. 178

Figure 80: $^1$H Spectrum of 3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. 70 .................................................................................................................... 179

Figure 81: $^{13}$C Spectrum of 3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. 70 .................................................................................................................... 180

Figure 82: $^1$H Spectrum of N-[2-(2-Isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide 71 .................................................................................................................... 181

Figure 83: $^{13}$C Spectrum of N-[2-(2-Isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide 71 .................................................................................................................... 182

Figure 84: $^1$H Spectrum of tert-butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-enylethylnyl)phenylcarbamate 72 .................................................................................................................... 183

Figure 85: $^{13}$C Spectrum of tert-butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-enylethylnyl)phenylcarbamate 72 .................................................................................................................... 184

Figure 86: $^1$H Spectrum of 4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 48 .................................................................................................................... 185

Figure 87: $^{13}$C Spectrum of 4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 48 .................................................................................................................... 186

Figure 88: $^1$H Spectrum of 9-Benzyl-2,3-diisopropoxy-9H-carbazole-1,4-dione 69 .................................................................................................................... 187
**Figure 89**: $^{13}$C Spectrum of 9-Benzyl-2,3-diisopropoxy-$9H$-carbazole-1,4-dione 69 ...................................................................................................................... 188

**Figure 90**: $^1$H Spectrum of 4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 88 ........................................................................................................... 189

**Figure 91**: $^{13}$C Spectrum of 4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 88 ........................................................................................................... 190

**Figure 92**: $^1$H Spectrum of 1-Benzyl-5,6-diisopropoxy-2,3-dihydro-$1H$-indole-4,7-dione 91 .......................................................................................................................... 191

**Figure 93**: $^{13}$C Spectrum of 1-Benzyl-5,6-diisopropoxy-2,3-dihydro-$1H$-indole-4,7-dione 91 .......................................................................................................................... 192

**Figure 94**: $^1$H Spectrum of 5,6-Diisopropoxy-2,3-dihydro-$1H$-indole-4,7-dione 93 .......................................................................................................................... 193

**Figure 95**: $^{13}$C Spectrum of 5,6-Diisopropoxy-2,3-dihydro-$1H$-indole-4,7-dione 93 .......................................................................................................................... 194

**Figure 96**: $^1$H Spectrum of 1-Benzyl-5,6-diisopropoxy-$1H$-indole-4,7-dione 94 .......................................................................................................................... 195

**Figure 97**: $^{13}$C Spectrum of 1-Benzyl-5,6-diisopropoxy-$1H$-indole-4,7-dione 94 .......................................................................................................................... 196

**Figure 98**: $^1$H Spectrum of tert-butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-etyl)but-3-ynyl carbamate 89 .............................................................................. 197

**Figure 99**: $^{13}$C Spectrum of tert-butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-etyl)but-3-ynyl carbamate 89 .............................................................................. 198

**Figure 100**: $^1$H Spectrum of tert-butyl benzyl-2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethyl carbamate 92 .................................................................................... 199

**Figure 101**: $^{13}$C Spectrum of tert-butyl benzyl-2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethyl carbamate 92 .................................................................................... 200

**Figure 102**: $^1$H Spectrum of 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone 51a .................................................................................... 201

**Figure 103**: $^{13}$C Spectrum of 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone 51a .................................................................................... 202
**Figure 104:** $^1$H Spectrum of 2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione 51d

**Figure 105:** $^{13}$C Spectrum of 2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione 51d

**Figure 106:** $^1$H Spectrum of 2,3-diisopropoxy-5-(2-nitrophenyl)cyclohexa-2,5-diene-1,4-dione 51c

**Figure 107:** Expanded view of gHMBC Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35a

**Figure 108:** Expanded view of gHMQC Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35a
List of Schemes

Scheme 1: Skraup Quinoline Synthesis ..............................................................2
Scheme 2: Doebner-von Miller Quinoline Synthesis ........................................... 3
Scheme 3: Knorr Quinoline Synthesis.................................................................4
Scheme 4: Conrad-Limpach Quinoline Synthesis ..............................................4
Scheme 5: Similarities of the Conrad-Limpach and Knorr Quinoline Synthesis ...5
Scheme 6: Friedländer Quinoline Synthesis ..................................................... 6
Scheme 7: Pfitzinger Quinoline Synthesis...........................................................7
Scheme 8: Ruthenium Catalyzed Quinoline Synthesis .......................................8
Scheme 9: Microwave Assisted Quinoline Synthesis .......................................8
Scheme 10: Natural Products Synthesized from Squarate Derivatives ..........10
Scheme 11: Synthesis of Assoanine from Dimethyl Squarate .........................11
Scheme 12: Initially Planned Reaction Sequence ...........................................13
Scheme 13: General Reaction Sequence for the Synthesis of Novel Quinolines ........................................................................................................... 13
Scheme 14: Proposed Mechanism for the Formation of the Alkylidene ............15
Scheme 15: Synthesis of the N-BOC Protected Starting Materials .................19
Scheme 16: Alkylation of Diisopropyl Squarate.................................................20
Scheme 16a: Alkylation of Diisopropyl Squarate with other N-BOC Protected Derivatives ........................................................................................................ 22
Scheme 17: Alternate Method for the Synthesis of Alkylation Products .............23
Scheme 18: Expansion, Deprotection and Reduction of BOC Protected Derivatives .................................................................................................................25
Scheme 19: Air Oxidation of the Quinolinol.......................................................26
Scheme 20: Reaction Sequence for the Semisquarate Derivative.......................27
Scheme 21: Alkylation Diisopropyl Squarate with 45 .......................................28
Scheme 22: Alkylation Diisopropyl Squarate with 47 .......................................28
Scheme 23: Sonogashira Coupling of the Acetanilide (49) and N-benzyl (50) Derivatives ...............................................................................................................................30
Scheme 24: Thermal Ring Expansion of the Acetonilide.................................30
Scheme 25: Sonogashira Coupling of 2-Iodonitrobenzene ..............................32
Scheme 26: Thermal Ring Expansion of Nitrobenzene Derivative ....................32
Scheme 27: Thermal Ring Expansion of a Cyclobutenone Substituted Indole...35
Scheme 28: Base Mediated Indolization ...........................................................36
Scheme 29: Copper Mediated Indolization .......................................................36
Scheme 30: Copper Acetate Catalyzed Indolization .........................................37
Scheme 31: Palladium Catalyzed Indolization ..................................................38
Scheme 32: N-Iodosuccinimide Mediated Ring Expansion ...............................39
Scheme 33: N-Chlorosuccinimide Mediated Ring Expansion ...........................39
Scheme 34: Palladium Catalyzed Ring Expansion............................................40
Scheme 35: Base Mediated Indolization ...........................................................41
Scheme 36: Copper Mediated Reaction Scheme for N-BOC Protected 28a......42
Scheme 37: Copper Iodide Mediated Indolization for N-Benzyl Protected 48 . 44
Scheme 38: Copper Acetate Catalyzed Indolization .........................................45
Scheme 39: Attempted N-Iodosuccinimide Mediated Ring Expansion ..........46
Scheme 40: Attempted $N$-Chlorosuccinimide Mediated Ring Expansion ..........47
Scheme 41: Halide Mediated Cyclobutenone Rearrangement .........................47
Scheme 42: Existing Synthesis of *Drupella fragum* Indoloquinones 79 and 82 .................................................................51
Scheme 43: Alkylation of 27 with 83 and 87 ..................................................52
Scheme 44: Ring Expansion and Cyclization of 89 to 91 .................................53
Scheme 45: Proposed Mechanism for the Tandem Expansion/Cyclization of 89 ........................................................................................................................54
Scheme 46: Debenzylation of 91 .........................................................................55
Scheme 47: DDQ Oxidation of 91 to 94 ............................................................55
Scheme 48: Proposed Route for the Synthesis of 79 .........................................56
Scheme 49: Ring Expansion of 89 to Quinone 92 .............................................56
Scheme 50: Acidic Deprotection of 92 to 91 ............................................................57
Scheme 51: Proposed Future Research with Butyne Derivatives ......................57
List of Tables

Table 1: Summary of NMR Data for the Structural Determination of 35a ............. 14
Table 2: Alkylation Conditions of 26a to give 28a ............................................... 20
Table 3: Alkylation Conditions for 47 ................................................................. 29
Table 4: Copper Mediated Reaction Conditions for 28a ...................................... 43
Table 5: Copper Mediated Reaction Conditions for 28a .................................... 94
Part I

A Novel Entry to Cyclopenta[b]quinolines via Thermal Ring-Expansion of (2-Aminophenyl)-Ethynyl-Substituted Cyclobutenone Derivatives

1. Introduction

Quinoline derivatives are found in a significant number of natural products and pharmaceuticals. These alkaloids exhibit a wide array of biological activities including antimalarial, antibacterial, antidiabetic, anti-inflammatory and antitumor behaviors. Examples of biologically active quinolines are quinine and 20-(S)-camptothecin. Quinine (1) and 20-(S)-camptothecin (2) exhibit antimalarial and excellent antitumor activities, respectively (Figure 1).

Figure 1: Biologically Active Quinolines

Due to the significant biological activity exhibited by quinolines, development of novel synthetic methods of the quinoline core is of great interest to researchers.
Classical syntheses of quinolines typically fall into one of two major classes, cyclization of monosubstituted benzenes, usually \(N\)-substituted anilines, and cyclizations of ortho-disubstituted benzenes. The first class includes the Skraup, Doebner-von Miller, Knorr and Conrad-Limpach reactions as well as numerous modifications thereof and several less utilized reactions.\(^5\) The second major class of quinoline syntheses involves either an intramolecular or intermolecular condensation of ortho-disubstituted benzenes. These synthetic methods include the Friedländer and Pfitzinger reactions in addition to several minor variations.\(^5\)

1.1. Quinoline Syntheses: Intramolecular Cyclization of Anilines

The Skraup\(^6\) reaction is one of the oldest methods for the synthesis of quinolines.\(^5\) For example, quinoline (5) was obtained in moderate yield by heating aniline (3), glycerol (4) and sulfuric acid in nitrobenzene (Scheme 1). This reaction sequence occasionally suffers from the disadvantage of proceeding with extreme violence.\(^5,7\) Moderators such as acetic or boric acid were eventually added to avoid the fierce nature of these reactions. The reaction is thought to proceed through a Schiff base from the condensation of acrolein, generated \textit{in situ}, with aniline followed by acid mediated cyclization. Acrolein is known to be the product of acidic treatment of glycerol.\(^7\)

\textbf{Scheme 1: Skraup Quinoline Synthesis}

\[
\text{\textbf{Scheme 1: Skraup Quinoline Synthesis}} \\
\text{3} + \text{4} \xrightarrow{\text{H}_2\text{SO}_4, \text{nitrobenzene, } \Delta} \text{5 (60%)}
\]
Doebner and von Miller\textsuperscript{8} modified the Skraup procedure by substituting ethylene glycol (6) for glycerol. 2-Methylquinoline (7) was prepared in good yield by the apparent Michael addition of the aniline to crotonaldehyde formed \textit{in situ} from ethylene glycol (Scheme 2).\textsuperscript{7} Crotonaldehyde is formed via aldol condensation of acetaldehyde in turn formed from ethylene glycol. Mechanistically, the Doebner von-Miller is similar to the Skraup reaction.

\textbf{Scheme 2: Doebner-von Miller Quinoline Synthesis}

\[ \text{Scheme 2: Doebner-von Miller Quinoline Synthesis} \]

\[ \begin{array}{c}
\text{NH}_2 \\
\text{N} \\
\text{HO} \\
\text{OH}
\end{array} \] + \[ \begin{array}{c}
\text{H}_2\text{SO}_4 \\
\text{nitrobenzene, } \Delta
\end{array} \] \[ \rightarrow \begin{array}{c}
\text{7 (75%)}
\end{array} \]

The Knorr\textsuperscript{9} quinoline synthesis was the first cyclization involving an acetanilide intermediate. Knorr was able to demonstrate his reaction sequences were applicable to acetoacetylated aryl amines with vacant ortho positions. For example, 2-hydroxy-4-methylquinoline (9) was formed in good yield from the reaction of ethyl acetoacetate (8) with aniline (Scheme 3). Formation of the acetanilide intermediate is fairly straightforward. The aniline nitrogen attacks the ester carbonyl of the $\beta$-ketoester, which loses an equivalent of alcohol and forms the acetanilide. Cyclization and dehydration is brought about by the heating of the acetanilide in the presence of acid, forming a quinolone intermediate. The quinolone then tautomerizes to produce a hydroxyquinoline.\textsuperscript{10}
Conrad and Limpach\textsuperscript{11} developed a milder approach to quinoline formation with regiochemical outcomes different from the Knorr reaction. 4-Hydroxy-2-methylquinoline (10) was obtained in moderate yield from the acid catalyzed reaction of aniline and ethyl acetoacetate (Scheme 4).\textsuperscript{12} The aniline nitrogen condenses with the $\beta$-carbonyl carbon of the $\beta$-ketoester to form an enamine intermediate. Two mechanisms have been suggested for the formation of the quinoline upon heating. The first mechanism involves enolization of the enamine, $6\pi$ electrocyclization, loss of alcohol and tautomerization. The second mechanism suggested involves the loss of alcohol to give a ketene, $6\pi$ electrocyclization and tautomerization.\textsuperscript{10}

The regiochemical outcome of the Conrad-Limpach reaction can be affected by the careful adjustment of the reaction conditions. The anilide (11) and enamine
(12) could be interconverted in the presence of an acid catalyst and an appropriate drying agent at room temperature or by gentle heating. However, the Conrad-Limpach enamino-ester intermediate (12) cannot be converted to the Knorr regiochemistry with direct acidic treatment (Scheme 5). Heating 12 produces 4-Hydroxy-2-methylquinoline (10). Acid mediated cyclization and dehydration of 11 produces 9a, which tautomerizes to 9.

**Scheme 5: Similarities of the Conrad-Limpach and Knorr Quinoline Synthesis**

1.2. Quinoline Syntheses: Cyclization of Ortho-Disubstituted Benzenes

The Friedländer synthesis typically involves the condensation of an ortho-amino aldehyde or ketone with another aldehyde or ketone to produce the quinoline core. This reaction sequence is somewhat limited in scope since the ortho-amino benzaldehydes are susceptible to self condensation. An intermediate (15) in a synthesis of mappicine was prepared in excellent yield using a protected 2-aminobenzaldehyde 13 and ketone 14 (Scheme 6). Two mechanisms have been
proposed for the Friedländer reaction. The first proposed mechanism proceeds through the formation of the imine followed by an intramolecular Claisen condensation. The second mechanism proposed an intermolecular Claisen condensation followed by cyclization via imine formation.\(^\text{10}\)

**Scheme 6: Friedländer Quinoline Synthesis**

\[
\begin{align*}
&\text{CHO} & &\text{NHBoc} \\
&\text{NHBOc} & &\text{CHO} \\
&\text{BnO} & &\text{OAcOH, 100 °C} \\
\end{align*}
\]

\[\text{13} + \text{14} \rightarrow \text{15} (85\%)\]

Pfitzinger\(^\text{14}\) improved the Friedländer synthesis by the use of isatin (16) which is significantly more stable than the Friedländer starting materials.\(^\text{10}\)

2-Methylquinoline-4-carboxylic acid (18) was synthesized in excellent yield through a Friedländer type reaction (Scheme 7).\(^\text{15}\) The mechanism probably proceeds via isatic acid (17), is formed from base mediated ring opening of isatin (16), followed by an intermolecular condensation to form a Schiff base, usually with acetone. Cyclization of the Schiff base via Claisen condensation occurs between the benzylic carbonyl and the \(\alpha\)-methylene of the imine intermediate.\(^\text{10}\)
Scheme 7: Pfitzinger Quinoline Synthesis

1.3. Modern Quinoline Syntheses

More modern syntheses have been developed which are significantly milder than the “witch’s brews” of many of the classical methods. A catalytic ruthenium-grafted hydrotalcite (HT) route has been developed. This method uses an amino benzyl alcohol (19), an acetophenone (20) in the presence of molecular oxygen. 2-Substituted quinolines are formed from this reaction. As an example, compound 21 was formed in good yield. This reaction is superior to the Friedländer reaction since the starting materials are more stable. This is also the first reported example one-pot quinoline synthesis using heterogeneous catalysts. The catalyst was formed by mixing a dilute solution of RuCl₃ₙH₂O with hydrotalcite (Mg₆Al₂(OH)₁₆CO₃) and triethylamine. During the development of this catalyst system it was noticed that no reaction occurred in the absence of an amine (designated as N) or the ruthenium (Scheme 8).¹⁶
Scheme 8: Ruthenium Catalyzed Quinoline Synthesis

Microwave-assisted reaction technology of small organic molecules has become an attractive tool in organic synthesis. Microwave reactors are simple to operate and significantly enhance reaction rates. A three-component one-pot quinoline synthesis has been developed using aryl aldehydes, aryl amines and alkynes. Brief pulsed microwave irradiation of 22, 23 and 24 in the presence of a copper (I) salt impregnated montmorillonite clay gave the complex quinoline (25) in excellent yield (92%) (Scheme 9). In the absence of the montmorillonite clay the reactions typically produced poor yields.

Scheme 9: Microwave Assisted Quinoline Synthesis

1.4. Cyclobutenediones

Cyclobutenediones, “squarate” derivatives, have been shown to be highly versatile C₄-synthons that can undergo thermal rearrangement. These building
blocks and have been utilized for the synthesis of many polysubstituted cyclic compounds including heterocycles.\textsuperscript{17} Thermally induced ring-expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones are known to produce both 1,4-benzoquinones and 5-alkylidenecyclopentenediones.\textsuperscript{18} In general, alkyl-substituted alkynes offer clean conversion to quinones,\textsuperscript{19} whereas TMS-alkyne, alkynes with electron-withdrawing groups or alkenyl-substituted alkynes affords only 5-membered products. Alkynes with electron-donating groups, and aryl-substituted alkynes afford mixtures of 5- and 6-membered rings. Several natural products such as assoanine,\textsuperscript{19f} perezone, isoperezone,\textsuperscript{20} echinochrome A\textsuperscript{21} and pentalenene\textsuperscript{22} have been synthesized from squaric acid derivatives (Scheme 10). An example of the squarates being used in an alkylation ring expansion fashion is the synthesis of assoanine. Dimethyl squarate 25b was alkylated with propargyl alkyne 25a to give 25c in 87\% yield. Thermal ring expansion and cyclization in p-xylene at 138 °C yielded the tetracyclic hydroxyquinone intermediate 25d in 40\% yield. Subsequent conversion to the diphosphonate ester followed by reduction gave assoanine in 18\% yield over two steps (Scheme 11). Due to the versatility of the squarates we sought to use them to synthesize novel heterocycles.
Scheme 10: Natural Products Synthesized from Squarate Derivatives

- **Assoanine**
  - $R=\text{Me}$

- **Pentalenene**
  - $R=\text{i-Pr}$

- **Perezone**
  - $R=\text{t-Bu}$

- **Isoperezone**
  - $R=\text{t-Bu}$

- **Echinochrome A**
  - $R=\text{i-Pr}$
Scheme 11: Synthesis of Assoanine from Dimethyl Squarate

\[ 1) \text{n-BuLi, THF, } -78 \, ^\circ\text{C} \]
\[ 2) \text{, THF, } -78 \, ^\circ\text{C} \]

\[ 25a \rightarrow 25b \rightarrow 25c (87\%) \] 

\[ \text{p-xylene, } 138 \, ^\circ\text{C} \]

\[ 25d (40\%) \]

assoanine \[ 25e (18\%) \text{ two steps} \]

2. Results and Discussion

Thermal reactions of alkyne substituted cyclobutenone derivatives were examined as a part of a larger project to prepare complex heterocyclic compounds. We envisioned a synthesis proceeding via a ring-expansion of 4-hydroxy-2-cyclobuten-1-ones having heteroatoms tethered to the cyclobutenone in the 4-position via an alkyne (Scheme 12).
2.1. N-BOC Protected Derivatives

In our initial reaction, compound 28a was obtained via dilithiation of the N-protected 2-aminophenylalkyne 26a followed by alkylation with 2,3-bis(1-methylethoxy)-2-cyclobuten-1,4-dione (diisopropyl squarate 27). Cyclobutenone 28a was dissolved in toluene and heated at reflux overnight. Workup and purification by chromatography on silica gel gave a new compound initially thought to be the 1,4-quinone 29 based on NMR data. Deprotection of the putative compound produced a new product seemingly derived from the formation of a quinone-imine 31. However, upon attempted sodium borohydride reduction of 31, the spectral data of the product did not correspond to the expected hydroxycarbazole 32. A new methine having a carbon resonance at 68.9 ppm and its corresponding proton resonance at 5.05 ppm was observed. These resonances cannot be assigned to any of the carbons or protons expected for hydroxycarbazole 32. Submitting the reduction product to gHMQC (gradient Heteronuclear Multiple Quantum Coherence, one bond $^1$H and $^{13}$C hetero-correlation) (Figure 2) and gHMBC (gradient Heteronuclear Multiple Bond Coherence, two to four bond $^1$H and $^{13}$C hetero-correlation) (Figure 3) NMR experiments revealed that the product was in fact the fused quinolinol 35a and not the hydroxycarbazole 32. The $^1$H, $^{13}$C, gHMBC and gHMBC data are summarized in Table 1. This in turn means that the ring-expansion did not yield the 1,4-quinone 29 but its five-membered counterpart 33a. It should be noted that, this reaction was very selective with regard to ring-size. Only the five-membered ring was observed by $^1$H NMR of the crude reaction mixture and the
purified product. Subsequent removal of the BOC group gave the fused quinoline 34a and reduction yielded the fused quinolinol 35a (Scheme 13).

**Scheme 12: Initially Planned Reaction Sequence**

\[
\begin{align*}
26a & \xrightarrow{1) \text{nBuLi}} 27 & \xrightarrow{2) \text{heat}} 28a (64\%) & \xrightarrow{\text{H}^+} 29 (82\%)
\end{align*}
\]

\[
\begin{align*}
30 & \xrightarrow{\text{NaBH}_4} 31 (74\%) & \xrightarrow{\text{NaBH}_4} 32 (84\%)
\end{align*}
\]

**Scheme 13: General Reaction Sequence for the Synthesis of Novel Quinolines**

\[
\begin{align*}
28a & \xrightarrow{\text{heat}} 33a (82\%) & \xrightarrow{\text{H}^+} 35a (84\%)
\end{align*}
\]

\[
\begin{align*}
34a (74\%) & \xrightarrow{\text{NaBH}_4} 35a (84\%)
\end{align*}
\]
Table 1: Summary of NMR Data for the Structural Determination of 35a

<table>
<thead>
<tr>
<th>Position</th>
<th>$\delta_\text{C}$</th>
<th>$\delta_\text{H}$</th>
<th>HMBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68.9</td>
<td>5.05 s</td>
<td>C-2, C-3, C-9a, C-3a, C-9</td>
</tr>
<tr>
<td>2</td>
<td>159.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>151.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>131.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>126.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>128.0</td>
<td>7.64 d</td>
<td>C-8a, C-7, C-4a, C-8</td>
</tr>
<tr>
<td>6</td>
<td>124.9</td>
<td>7.36 t</td>
<td>C-8, C-4a, C-7</td>
</tr>
<tr>
<td>7</td>
<td>128.8</td>
<td>7.56 t</td>
<td>C-8a, C-5, C-9, C-8</td>
</tr>
<tr>
<td>8</td>
<td>128.6</td>
<td>7.97d</td>
<td>C-4a, C-6</td>
</tr>
<tr>
<td>8a</td>
<td>148.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>128.2</td>
<td>7.78 s</td>
<td>C-2, C-8a, C-9a, C-1, C-8, C-6, C-4a</td>
</tr>
<tr>
<td>9a</td>
<td>133.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: a) Correlations of $^1$H and $^{13}$C made by gHMOC (Figure 2)

The proposed mechanism of the ring expansion of 28a is depicted in Scheme 14. The mechanism probably proceeds through the electrocyclic ring opening of 28a to give ketene 29a followed by the 5-endo-dig cyclization forming intermediate 29d. Subsequent hydrogen atom abstraction followed to give the diradical 29e and later 5-alkylidencyclopentendione (33a). The anticipated mechanism for the ring expansion to give the 1,4-benzoquinones also depicted in Scheme 14. It should be noted that this mechanistic pathway did not occur since we did not observe the benzoquinone. The mechanism would probably proceed through the electrocyclic ring opening of 28a to give ketene 29a followed by the 6-endo-dig cyclization forming intermediate 29b. Subsequent hydrogen atom abstraction followed to give the diradical 29c and later 1,4-quinone formation (29).
Scheme 14: Proposed Mechanism for the Formation of the Alkylidene

\[
\begin{align*}
\text{28a} & \xrightarrow{5\text{-endo-dig}} \text{29a} \\
\text{29a} & \xrightarrow{6\text{-endo-dig}} \text{29b} \\
\text{29d} & \xrightarrow{} \text{29e} \\
\text{29e} & \text{33a}
\end{align*}
\]
Figure 2: Gradient Heteronuclear Multiple Quantum Coherence Spectrum of $^{35}$NHO$i$-Pr$i$-Pr$^{35}$a

- Pulse Sequence: HMQC
- Solvent: CDCl$_3$
- Temp: 25.6 C / 298.1 K
- INOVA-400 “Inova888”

- Relax. delay 1.039 sec
- Acq. time 0.142 sec
- Width 150.2 Hz
- 2D width 7009.7 Hz
- 4 repetitions
- 2 x 2% increments
- CALIBRATE n1, 399.465/9016 MHz
- REPOLICE 113.150.465/9016 MHz
- Diffusion off during acquisition
- off during delay
- w1 w255255 modulated
- DATA-PROCESSING
- Ghost suppression 8.266 sec
- F2 DATA-PROCESSING
- Ghost suppression 6.815 sec
- FT size 2048 x 4096
- Total time 40 min, 48 sec

35a
With this novel route to highly functionalized fused quinolines in hand the scope and limitations were examined. The starting materials were prepared from 2-iodoarylamines via a sequence of steps consisting of N-BOC protection of the amino group, Sonogashira coupling using ethynyl trimethylsilane and desilylation. The first three steps generally proceeded smoothly and often in excellent yield (Scheme 15). The N-BOC protection reactions proved best when the free aniline was treated with excess NaHMDS\textsuperscript{23} followed by the dropwise addition of a BOC\textsubscript{2}O/THF solution. Several other reaction conditions were attempted for the N-BOC protection of the anilines, but all gave poor yields of products. The Sonogashira\textsuperscript{24} reactions initially gave a significant amount of homocoupling of trimethylsilyl acetylene product which were hard to separate from the desired product. The homocoupling problem was alleviated by reducing the amount of the alkyne from 1.1 equivalents to 1.05 equivalents. The two methods\textsuperscript{65,25} used for the desilylation of the TMS-protected products (38b-38e), NaOH and KF. Deprotection using NaOH often gave higher yields however, the KF method was significantly faster. In addition, the KF method was superior to the NaOH method for the pyridine derivative (38e).
Scheme 15: Synthesis of the N-BOC Protected Starting Materials

\[
\begin{align*}
&\text{R} \text{I} \quad \text{X} \text{NH}_2 \\
&1) \text{NaHMDS, THF, rt} \quad 2) (\text{BOC})_2\text{O, THF, rt} \quad \text{Pd(PPh}_3\text{)}_2\text{Cl}_2, \text{CuI} \quad \text{NEt}_3, \text{rt}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>36b R=4-Cl, X=CH</td>
<td>37b</td>
<td>81%</td>
</tr>
<tr>
<td>36c R=5-OMe, X=C</td>
<td>37c</td>
<td>92%</td>
</tr>
<tr>
<td>36d R=5-Me, X=C</td>
<td>37d</td>
<td>88%</td>
</tr>
<tr>
<td>36e R=H, X=N</td>
<td>37e</td>
<td>60%</td>
</tr>
</tbody>
</table>

Notes:

The terminal alkynes were dilithiated and reacted with diisopropyl squarate. The alkylations were problematic and significant amounts of the alkyne starting material was often recovered (Scheme 16). One explanation for recovering significant amounts of the starting alkyne could be due to lower solubility of the dianion in the colder solutions. Multiple reaction conditions were investigated to optimize the alkylation conditions (Table 2).
Scheme 16: Alkylation of Diisopropyl Squarate

Table 2: Alkylation Conditions of 26a to give 28a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Reaction Conditions</th>
<th>Yield 28a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2.0 eq. n-BuLi</td>
<td>-78 °C, 20 min., then 27, -78 °C, 30 min.</td>
<td>48%</td>
</tr>
<tr>
<td>2a</td>
<td>2.5 eq. n-BuLi</td>
<td>-78 °C, 20 min., then 27, -78 °C – rt, 30 min.</td>
<td>62%c</td>
</tr>
<tr>
<td>3b</td>
<td>3.0 eq. n-BuLi</td>
<td>-78 °C, 20 min., then 27, -78 °C, 30 min.</td>
<td>NR</td>
</tr>
<tr>
<td>4b</td>
<td>2.5 eq. t-BuLi</td>
<td>-78 °C, 30 min., then 27, -78 °C – rt, 1h.</td>
<td>unidentifiable</td>
</tr>
<tr>
<td>5b</td>
<td>2.5 eq. t-BuLi</td>
<td>-78 °C, 30 min., then 27, -78 °C – rt, 30 min.</td>
<td>31%</td>
</tr>
<tr>
<td>6b</td>
<td>3.0 eq. t-BuLi</td>
<td>-78 °C, 1h., then 27, -78 °C - rt, 12h</td>
<td>unidentifiable</td>
</tr>
<tr>
<td>7b</td>
<td>2.5 eq. n-BuLi</td>
<td>-78 °C 1h, to -20 °C, 1h., then 27, -78 °C – rt, 1h.</td>
<td>unidentifiable</td>
</tr>
<tr>
<td>8a</td>
<td>2.5 eq. t-BuLi</td>
<td>-78 °C, 30 min., then 27, -78 °C – rt, 1h.</td>
<td>20%</td>
</tr>
<tr>
<td>9a</td>
<td>2.5 eq. NaHMDS</td>
<td>-78 °C, 1h, then 27, -78 °C, 18h.</td>
<td>NR</td>
</tr>
<tr>
<td>10a</td>
<td>2.5 eq. n-BuLi</td>
<td>-78 °C, 1h, then 27, CeCl₃, -78 °C, 1h.</td>
<td>NR</td>
</tr>
<tr>
<td>11b</td>
<td>2.5 eq. n-BuLi</td>
<td>-10 °C, 15 min., then 27, -10 °C, 30 min.</td>
<td>64%d</td>
</tr>
</tbody>
</table>

Notes: All reactions in this table used 1 equivalent of 26a and 27 a) The dilithiated aniline was added to the squaric acid derivative, b) The squaric acid derivative was added to the dilithiated aniline c) High yield obtained in one case, repeated reaction gave inconsistent results d) Consistent results
It should also be noted that adding two equivalents of the alkyne (26a) gave only a 64%, based on the converted squarate, yield of 28a. This reaction sequence was subsequently abandoned since only approximately 30% of the alkyne 26a was converted. It was discovered that the conditions of entry 11 gave the most consistent alkylation results. Therefore, these conditions were used without modification for the alkylation of the other derivatives (26b-26d) with the exception of the pyridine (26e). It was found that the pyridine derivative (28e) was obtained in slightly higher yields (approximately 10%) when allowed to warm to room temperature over the last 10 minutes of the reaction, prior to quenching. Upon alkylation of the 5-methoxy-substituted substrate (26c), an inseparable mixture of the expected alkylation product 28c and alkylation of the squarate 27 with excess butyl lithium was isolated (structure not shown) (Scheme 16). Alkylation of diisopropyl squarate (27) was only seen in the case of the 5-methoxy-substituted substrate (26c) (Scheme 16a).
Scheme 16a: Alkylation of Diisopropyl Squarate with other N-BOC Protected Derivatives

Note: a) Inseparable mixture with the butyl addition product of diisopropyl squarate, b) The reaction was warmed to room temp for 10 minutes prior to quench

The Sonogashira reaction was also briefly investigated as an alternative to deprotonation and alkylation of the N-protected ethynyl anilines. Squarate derivative\textsuperscript{27} \textsuperscript{39} was stirred briefly with 5% Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} and 5% CuI in triethylamine followed by the addition of N-protected aryl iodide \textsuperscript{37a} were allowed to stir overnight at room temperature. Unfortunately, a low yield of the anticipated product \textsuperscript{28a} was obtained. Addition of a full equivalent of CuI was found to increase the yields. Generally, the deprotonation route was better except in one case (Scheme 17). Apart from the anisole derivative \textsuperscript{28c} that was cleanly synthesized in 65% yield, the deprotonation-alkylation route gave a better yield of product. We were somewhat surprised that the toluene derivative (\textsuperscript{37d}) did not react under the Sonogashira reaction conditions.
Scheme 17: Alternate Method for the Synthesis of Alkylation Products

![Scheme 17](image)

Notes: a) 5% CuI added, b) 1 equivalent of CuI was added, c) based on recovered iodide

With a number of alkyne-cyclobutenones in hand the ring expansion to form cyclopenta[b]quinolines was examined (Scheme 18). Thermal ring-expansion of 28a-28e gave in all cases the expected cyclopentenediones 33a-33e. Toluene was found in general to be a good solvent for the ring expansions with the exception of the pyridine derivative. However, a cleaner conversion of the pyridine 33e was observed in 1,2-dichloroethane (1,2-DCE).\(^7\) Again, all thermal reactions were selective with regard to ring-size, and only five-membered rings were observed by \(^1\)H NMR. Acidic removal of the BOC-group and spontaneous cyclization gave the expected cyclopenta[b]quinoline-1-ones 34a-34e. The pyridine derivative (33e) proved to be more difficult to deprotect compared to the toluene (33d), anisole (33c) and chloro (33b) derivatives. HCl in EtOAc or HCl in MeOH for the N-deprotection of the pyridine derived compound yielded neither starting material nor any product. The use of TMSI\(^2\) is typically a very fast method for the removal of N-BOC groups, however, in the case of 33e only 3% of the fused aza-quinolone 34e was obtained. Trifluoroacetic acid in CH\(_2\)Cl\(_2\) at
reflux was the only successful deprotection of the pyridine and yielded the aza-quinolone 34e in 86% yield. Finally, sodium borohydride reduction of 34a-34e furnished the cyclopenta[b]quinoline-1-ols 35a-35e (Scheme 17). The reduction product 35e was not fully characterized due to rapid decomposition and was therefore only tentatively assigned as the aza-quinolinol. 

$^1$H NMR data was used to identify which stage the reactions were. We were able to identify the basic structures by observing the chemical shifts of the isopropyl methine (heptets) and the isopropyl methyls (doublets). Upon reduction we were also able to track the new methine formed. The typical range for the resonances of the alkylation products (28a-28e) ranged from 4.90-4.85 and 5.02 for the methine signals and 1.47-1.46 and 1.32-1.29 for the isopropyl methyls. For the ring expansion (33a-33e) the methine protons ranged from 5.61-5.55 as overlapping heptets, the methyl doublets overlapped with a range of 1.42-1.36. The quinolinone (43a-43e) methines ranged from 5.72-5.62 and 5.32-5.23 as separate signals, the methyl resonances ranged from 1.48-1.51 and 1.34-1.38 as separate signals. The quinolinol (35a-35d) methine signals ranged from 5.25-5.38 and 5.12-5.15 as separate signals and the methyls 1.37-1.34. The new methine for the reduction ranged from 5.01-5.06 ppm.
Scheme 18: Expansion, Deprotection and Reduction of BOC Protected Derivatives

Notes: a) In refluxing toluene, b) Yield calculated over two steps, c) refluxing 1,2-DCE, d) HCl was used for the deprotection e) TFA was used for the deprotection f) TMSI was used for the deprotection g) Tentative assignment due to rapid decomposition

The cyclopenta[b]quinoline-1-ols (35a-35d) were slowly oxidized to the corresponding cyclopenta[b]quinoline-1-ones (34a-34d) upon standing in air as determined via $^1$H NMR, the yields were not calculated for this oxidation (Scheme 19).
As a final example, 3-(1-methylethoxy)-4-methyl-3-cyclobutene-1,2-dione\textsuperscript{69} was reacted with the dianion formed from 26a to give the expected alkylation product 41 as a single regioisomer in 48\% (59\% based on recovered 26a). The alkylation occurred on the more electrophilic carbonyl carbon. The carbonyl in conjugation with the alkoxy-group is typically less reactive due to resonance contributions from the alkoxy oxygen. Ring-expansion of 41 in 1,2-DCE at reflux furnished the expected cyclopentendione 42 as an 8.3:1 E/Z (by NMR integration) mixture in 49\% overall yield. A poor yield of 42 was obtained in refluxing toluene. The E-isomer has previously been shown to be the kinetic product from ring-expansions of related compounds.\textsuperscript{29} Although condensation of the free amine with the carbonyl having a conjugated alkoxy-group is expected to be much slower, we were surprised to observe only one isomer (43) upon BOC-protecting group removal. The product is derived from cyclization of the thermodynamically more stable Z-isomer. This observation can be explained by a facile E to Z isomerization of the alkene prior to cyclization. Isomerization of E-42 to Z-42 was observed by $^1$H NMR simply by allowing the NMR sample to sit for a few hours at ambient temperature. Reduction of 43 gave 44 however, this compound was not fully characterized due to very rapid decomposition and was
only tentatively assigned as 44 (Scheme 20). $^1$H and $^{13}$C NMR spectra of 44 were in full agreement with the structure of 44.

**Scheme 20: Reaction Sequence for the Semisquarate Derivative**

2.2. *N*-Acetyl and *N*-benzyl aniline

As a subproject to the N-BOC protected anilines two additional amino protective groups were studied. Our goal was to test the theory that a change in the amino protecting group would affect the thermal ring expansion *i.e.* 5- versus 6-membered ring formation. The *N*-acetyl and the *N*-benzyl protective groups were studied. The *N*-acetyl $^{30}$ (45) and *N*-benzyl$^{31}$ (47) derivatives were synthesized according to literature procedures. Diisopropyl squarate (27) was alkylated by
the N-acetyl derivative (45) in 72% yield by the addition of the dianion to the squarate derivative. The yields were approximately 20% lower when the squarate was added to the dianion (Scheme 21). Alkylations using N-Benzyl aniline (47) proved to be very problematic and only poor yields were obtained (Scheme 22). Multiple conditions for the alkylation of the N-benzyl derivative (47) were investigated all giving disappointing results (Table 2). It should also be noted that alkylation of the free aniline (not depicted) gave unidentifiable products.

**Scheme 21: Alkylation of Diisopropyl Squarate with 45**

![Scheme 21](image)

**Scheme 22: Alkylation of Diisopropyl Squarate with 47**

![Scheme 22](image)

*Note: a) Yield based on recovered 47*
### Table 3: Alkylation Conditions for 47

<table>
<thead>
<tr>
<th>Trial</th>
<th>Base</th>
<th>Reaction Conditions</th>
<th>Yield of 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.05 eq. n-BuLi</td>
<td>-40 °C, 15 min., then 27, -40 °C, 30 min.</td>
<td>19%, 50%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>1.05 eq. n-BuLi</td>
<td>-10 °C, 15 min., then 27, -10 °C, 30 min.</td>
<td>24%, 39%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>2.05 eq. n-BuLi</td>
<td>-10 °C, 30 min., then 27, -10 °C - rt, 1h.</td>
<td>14%</td>
</tr>
<tr>
<td>4</td>
<td>1.7 eq. n-BuLi</td>
<td>-10 °C, 15 min., then 27, -10 °C - rt, 30 min.</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>1.7 eq. n-BuLi</td>
<td>-10 °C, 20 min., then 27, -10 °C - rt, 30 min.</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td>1.7 eq. n-BuLi</td>
<td>-10 °C, 20 min., then 27, -10 °C - rt, 1h.</td>
<td>21%, 26%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>1.1 eq. n-BuLi</td>
<td>-10 °C, 15 min., then 27, -10 °C - rt, 30 min.</td>
<td>23%</td>
</tr>
<tr>
<td>8</td>
<td>1.5 eq. n-BuLi</td>
<td>-10 °C, 15 min., then 27, -10 °C - rt, 30 min.</td>
<td>7%, 9%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>1.1 eq. NaHMDS</td>
<td>-10 °C, 10 min., then 27, -10 °C, 30 min.</td>
<td>10%, 12%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>1.1 eq. NaHMDS</td>
<td>-40 °C, 30 min., then 27, -40 °C, 1h.</td>
<td>9%, 12%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>1.1 eq. n-BuLi</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O, -78 – 0 °C, 30 min., then 27, Et&lt;sub&gt;2&lt;/sub&gt;O, 0 °C 30 min.</td>
<td>10%</td>
</tr>
</tbody>
</table>

**NOTE:** Yield based on recovered 47

The Sonogashira reaction was also briefly investigated for the N-acetyl and N-benzyl derivatives. Squarate derivative<sup>27</sup> (39) was briefly slurried with 5% Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, and one equivalent of Cul in triethylamine and then the protected aryl iodides were added and the resulting reaction mixture was allowed to stir overnight at ambient temperature. The coupling of the N-acetyl (49) and N-benzyl (50) derivatives gave the desired products in 45% and 4%, respectively. In both cases the deprotonation-alkylation procedure, especially in the N-acetyl case, was found to be a superior method (Scheme 23).
Scheme 23: Sonogashira Coupling of the Acetanilide (49) and N-benzyl (50) Derivatives

Note: a) Based on recovered 49

The alkylated N-acetyl protected compound 46 gave a good yield (72%) of alkyldiene 51 upon thermal ring expansion in toluene at reflux (Scheme 24). The N-benzyl alkylation product 48 on attempted thermal ring expansion yielded only unidentifiable products in toluene at reflux and did no reaction was observed in 1,2-DCE at reflux with no starting material being recovered. The N-benzyl derivative was not further examined.

Scheme 24: Thermal Ring Expansion of the Acetanilide
Although the yield of the ring-expanded N-acetyl protected product 51 was good, we were unable to remove the amino protecting group using dilute HCl at reflux or hydrazine at reflux.

2.3. Nitrobenzene Derivative

The functional group was changed from a N-protected aniline to a nitro group. This subproject examined the effect of the electron withdrawing group on the thermal ring expansion. Alkylation of 27 with ethynyl nitrobenzene did not give the expected product, instead the Sonogashira reaction was investigated for nitro derivative 51a. Squarate derivative 39 was stirred briefly with 5% Pd(PPh₃)₂Cl₂ and 5% CuI in triethylamine followed by the addition of 2-iodonitrobenzene 51b. Unfortunately, a 9% yield of the anticipated product 51a was obtained. Addition of a full equivalent of CuI was found to increase the yields to 53% 51a (Scheme 25). Thermal ring expansion gave two products, the quinone 51c in 11% yield and the alkylidene 51d in 33% yield (Scheme 26). The assignments were made based on the quinone and alkylidene protons, as compared to literature values of ring-expanded squarates.²⁹ The literature values reported for a squarate based alkylidene and quinone were a singlet at 7.41 ppm a singlet at 6.70 ppm, respectively. Compound 51d has a singlet at 7.69 ppm and 51c showed up at 6.47 ppm. The electron withdrawing group seems to have a greater selectivity for the 5-membered ring versus the 6-membered ring formation. We were pleased to discover the 6-membered ring can be obtained from aryl-alkyne ring
expansion, however we were disappointed in the subsequent yield of the quinone.

**Scheme 25: Sonogashira Coupling of 2-Iodonitrobenzene**

![Scheme 25](image)

**Scheme 26: Thermal Ring Expansion of Nitrobenzene Derivative**

![Scheme 26](image)

### 3. Conclusions

A novel route to cyclopenta[b]quinoline-1-ones and –ols has been developed. Substituted cyclopenta[b]quinolin-1-ones were prepared by thermal ring-expansion of substituted N-BOC protected 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones forming the corresponding 2-aminophenylmethylidene substituted 4-cyclopentene-1,3-diones. Deprotection of the amine resulted in spontaneous condensation to give cyclopenta[b]quinolin-1-ones. Sodium
borohydride reduction of these products produced cyclopenta[b]quinolin-1-ols. The key step in the sequence is a thermally induced ring-expansion of 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones. Changing the amino protecting group had no effect on the ring size selectivity of the thermal ring expansion. The thermal ring expansion of the nitro derivative suggests that electron withdrawing substituents may slightly alter the size selectivity of the ring formation.
Part II

Attempted Indolizations and Additional Ring Expansions

1. Introduction

Heterocycles play a central role in organic and medicinal chemistry since many of these compounds exhibit useful properties. The indole nucleus is found in a significant number of biologically active, naturally occurring products and are extremely valuable in medicinal chemistry. Common methods for indolization of 2-ethynylanilines include base, and transition metal mediated and catalyzed cyclizations.

Ring-expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones to give 5-alkyldenecyclopentenediones have been reported that use palladium complexes and electrophilic reagents such as N-iodosuccinimide, NIS, and N-chlorosuccinimide, NCS. We envisioned using these different indolization methods to form the indole nucleus followed by a ring expansion/cyclization sequence to afford carbazolequinones. We also wanted to use the ring expansion routes to tune the product ring size of the squarate portion of the molecules to afford either a 1,4-quinone or a alkylidene cyclopentendione. The synthesis of carbazolequinones using cyclobutenone substituted indoles has been reported (Scheme 27). Squarate 67a was alkylated with 67b. The reaction was quenched with acetic anhydride and worked up giving 67c.
Compound 67c was then immediately thermalized and oxidized with ceric ammonium nitrate, CAN, to give 67d as a single regioisomer.

**Scheme 27: Thermal Ring Expansion of a Cyclobutenone Substituted Indole**

1.1. Indolization Methods

Base mediated cyclization methods have been used extensively to form the indole nucleus. Silyl alkyne 52 was cyclized to give 53 (70% yield) in the presence of potassium tert-butoxide in tert-butanol at 83 °C (Scheme 28). The proposed mechanism involves the deprotonation of the carbamate nitrogen followed by attack on the alkyne forming a 2-trimethylsilyl 1-tert-butoxycarbonylindole intermediate. Subsequent hydrolysis cleaves the tert-butoxycarbonyl and trimethylsilyl groups.
In the early 1960s Castro et al. developed copper (I) mediated methods for the cyclization of aminoalkynes to produce indoles. The 2-substituted indole \( 55 \) was synthesized in the presence of CuI (2 equivalents) in DMF at 136 °C in 45% yield (Scheme 29). The mechanism probably involves the copper complexing with the alkyne followed by intramolecular attack by the amino group. The subsequent steps likely involve a proteolytic cleavage of an intermediate \( \sigma \)-alkenylcopper complex forming the indole nucleus.

Copper acetate has also been used to catalyze the formation of the indole nucleus from various \( N \)-protected ethynylamines. The indole moiety in a synthesis of hippadine (58) was formed in 80% yield by copper (II) acetate.
catalysis in 1,2-DCE at 83 °C (Scheme 30). The mechanism is thought to be
similar to the CuI reactions.  

**Scheme 30: Copper Acetate Catalyzed Indolization**

Palladium (II) complexes can also catalyze the amination and cyclization of
alkynes to form the indole core.  An indole intermediate 60 in the synthesis of
61 was formed via palladium catalyzed amination of the alkyne (Scheme 31).  
Compound 61 is known to suppress apoptosis in human cells. The mechanism
probably involves the coordination of the palladium to the alkyne followed by an
intramolecular attack by the amino group to form the metallo-indole intermediate.
The subsequent steps probably involve a proteolytic cleavage of the intermediate
σ-alkenylpalladium complex thus forming the indole nucleus.
1.2. Electrophilic Ring Expansions 4-Hydroxy-2-cyclobuten-1-ones

*N*-iodosuccinimide (NIS) mediated ring expansion has been used to form 5-alkylidenecyclopentenediones from 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones. The electrophilic ring expansion of 62 in the presence of excess NIS gave alkyldiene 63 in 44% yield (Scheme 32). Two mechanisms have been suggested. The first step likely involves an I⁺ transfer to the hydroxyl group to form a hypoiodite intermediate. This intermediate then probably induces a 1,2-acyl migration to the alkyne followed by the iodination forming the iodoalkylidene 63. The other possible mechanism involves the formation of an iodonium ion with the alkyne followed by a 1,2-acyl migration forming 63.⁴⁷
Scheme 32: N-Iodosuccinimide Mediated Ring Expansion

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{EtO} & \quad \text{OH} \\
n-\text{Bu} & \quad \text{NIS} \\
\text{CH}_3\text{CN} & \\
\longrightarrow \\
\text{EtO} & \quad \text{EtO} \\
\text{I} & \quad \text{EtO} \\
n-\text{Bu} &
\end{align*}
\]

62 \quad \text{63 (44%)}

\(N\)-chlorosuccinimide (NCS) has recently been used in ring expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones. Quinones 65a and 65 were produced in 40% and 35%, respectively. The mechanism is likely to involve thermal ring-expansion followed by radical chlorination of the diradical intermediate (Scheme 33).

Scheme 33: N-Chlorosuccinimide Mediated Ring Expansion

\[
\begin{align*}
\text{Pri-O} & \quad \text{Pri-O} \\
\text{Pri-O} & \quad \text{OH} \\
\text{PhCH}_3, 150 \degree \text{C} & \quad \text{NCS} \\
\longrightarrow \\
\text{Pri-O} & \quad \text{Pri-O} \\
\text{Cl} & \quad \text{Pri-O} \\
\text{Pri-O} & \quad \text{Pri-O}
\end{align*}
\]

64 \quad \text{65a (40%)} \quad \text{65 (35%)}

Palladium catalyzed ring expansion of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones to form 5-alkylidenecyclopentenediones has also been investigated. Compound 67 was prepared in moderate yield (45%) with an E:Z ratio of isomers of 12:1. The E-isomer was found to be thermodynamically more stable. This reaction was very selective with regard to ring size and only five membered rings were obtained. The mechanism likely involves the coordination of the palladium to the
alkyne followed by 1,2-acyl migration and proteolytic cleavage of the σ-alkenylpalladium complex forming the alkylidene. The hydroxyl group is more likely to stabilize the positive charge left from the palladium induced 1,2-acyl migration (Scheme 34).

**Scheme 34: Palladium Catalyzed Ring Expansion**

![Scheme 34](image)

2. Results and Discussion

In the following paragraphs the base mediated, transition metal mediated and catalyzed reactions of heteroatom tethered 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones and electrophilic ring expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones will be discussed. We envisioned a cyclization route to the indole nucleus and later ring expansion/cyclization of the 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones to form the 1,4-quinone instead of the previously synthesized 5-alkylidenecyclopentenediones. Several different methods for indole core and quinone formation were attempted. The methods tried were aimed at the formation of the indole nucleus and subsequent ring expansion to eventually form carbazolequinones.

The first set of these reactions, discussed above, included base mediated, copper mediated, copper and palladium catalyzed conditions. Electrophilic
methods were attempted to affect the ring expansion of the cyclobutenone moiety. The second set of reactions, discussed above, included \( N \)-iodosuccinimide mediated, \( N \)-chlorosuccinimide mediated and palladium catalyzed ring expansions.

2.1. Base Mediated Indole Formation

The BOC protected alkylation product \( 28a \) was heated in dry \( t \)-BuOH at 83 \(^{\circ}\)C in the presence of \( t \)-BuOK forming indole \( 68 \) in 20\% yield. An explanation of this observation is that the base deprotonated the hydroxyl group of \( 28a \) and induced a retro-alkylation. There was no evidence of the cyclobutenone moiety in the crude mixtures or in the purified products. It should be noted that the indole core was actually formed. No reaction occurred when \( t \)-BuOK or KH in NMP were used. \( N \)-acetyl derivative \( 46 \) was also reacted under the same conditions but yielded only unidentifiable products (Scheme 35). Based on this disappointing result no other base mediated indolizations were attempted.

Scheme 35: Base Mediated Indolization

\[
\begin{align*}
\text{unidentifiable products} & \xrightarrow{t \text{-BuOK}, t \text{-BuOH}, \text{reflux, } R=\text{BOC}} 28a \quad R=\text{BOC} \\
& \xrightarrow{t \text{-BuOK}, t \text{-BuOH}, \text{reflux, } R=\text{Ac}} 46 \quad R=\text{Ac} \\
& \xrightarrow{t \text{-BuOK}, t \text{-BuOH}, \text{reflux, } R=\text{BOC}} 68 \quad (20\%)
\end{align*}
\]
2.2. Attempted Copper Mediated Indole Formation

Examples of an attempted copper mediated indolization reaction are shown in Scheme 36 and Scheme 37. The reaction conditions attempted for the \(N\)-BOC protected 28a are summarized in Table 4. The yields were not corrected for the recovered starting material. In contrast to the reaction of the free amine shown in Scheme 25 \(N\)-BOC protection appears to inhibit the reaction. It seems that these reactions are simply thermal ring expansions of the cyclobutenone portion of the molecule. The copper mediated reactions were not attempted on the other \(N\)-BOC (28b-28e) or the \(N\)-acetyl 46 derivatives.

**Scheme 36: Copper Mediated Reaction Scheme for \(N\)-BOC Protected 28a**
Table 4: Copper Mediated Reaction Conditions for 28a

<table>
<thead>
<tr>
<th>Temperature/Time</th>
<th>Cui (2 eq.)</th>
<th>33a</th>
<th>Recovered 28a</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 °C/24h</td>
<td>Yes</td>
<td>No Reaction</td>
<td>Not Calculated</td>
</tr>
<tr>
<td>85 °C/24h</td>
<td>Yes</td>
<td>8%</td>
<td>24%</td>
</tr>
<tr>
<td>100 °C/6h</td>
<td>Yes</td>
<td>11%</td>
<td>Not recovered</td>
</tr>
<tr>
<td>120 °C/1h</td>
<td>Yes</td>
<td>11%</td>
<td>32%</td>
</tr>
<tr>
<td>120 °C/1h</td>
<td>No</td>
<td>23%</td>
<td>18%</td>
</tr>
</tbody>
</table>

The CuI mediated reaction (Scheme 37) on the N-benzyl derivative 48 appears to undergo both thermal ring expansion leading to 35a and metal mediated indolization-ring expansion-cyclization sequence leading to 69. The formation of carbazolequinone 69 likely involves the copper coordinating with the alkyne followed by an intramolecular attack of the amine forming a metallo-indole intermediate. Subsequent acyl migration to form a metallocycle and then reductive elimination would form carbazolequinone 69. Quinoline 35a is likely formed from the thermal ring expansion of the cyclobutenone portion followed by the intramolecular iminium ion formation. It is likely that the benzyl group was removed from the iminium ion by a free iodide ion thus forming the quinoline 35a. It should be noted that it is not clear whether the CuI affects any of the fore-mentioned ring expansion. This portion of the project was also abandoned since 48 was difficult to synthesize (Table 3, Scheme 22) and the reaction gave low yields.
Scheme 37: Copper Iodide Mediated Indolization for \(N\)-Benzyl Protected 48

\[
\begin{align*}
\text{Scheme 37: Copper Iodide Mediated Indolization for } \text{N-Benzyl Protected 48} \\
\end{align*}
\]

2.3. Copper Acetate Catalyzed Indole Formation

Copper acetate catalyzed indole formation was attempted on derivatives 28a and 46. To our surprise the reaction on \(N\)-BOC protected compound 28a cleaved the molecule into precursor alkyne and squaric acid derivative. The alkyne and squaric acid were recovered in 55% and 85%, respectively. On the other hand, \(N\)-acetyl compound 46 was cyclized to give the novel indole 70 in 72% yield (Scheme 38). The rearrangement of the squarate moiety is likely a consequence of acetic acid being liberated from the reaction. Acid catalyzed rearrangements of this type have been reported. In the future this rearrangement could potentially be avoided by the addition of a mild scavenger base. This indolization reaction sequence was not attempted on other \(N\)-BOC (28b-28e) and \(N\)-benzyl (48) derivatives. The copper acetate catalyzed reactions were abandoned for the \(N\)-BOC case since the desired products, the indole moiety, were not obtained.
2.4. Attempted Palladium Catalyzed Indole Formation or Ring Expansions

Reaction of 28a and 48 with a number of palladium catalysts were examined. The catalysts used include bis(triphenylphosphine)palladium dichloride and bis(benzonitrile)palladium dichloride. The free amine might be a better choice for this reaction, but we were unable to prepare this compound. The palladium catalyzed reactions were not attempted on the other \(N\)-BOC (28b-28e) or \(N\)-acetyl (46) derivatives. The palladium catalyzed reactions were abandoned since the desired products, the indole moiety, were not obtained.

2.5. \textit{N}-Iodosuccinimide Mediated Ring Expansion

\textit{N}-Iodosuccinimide mediated ring expansions were attempted on 28a, 46 and 48. Two different reaction conditions were used for the 28a and 46. The first set of reaction conditions were tried on all three protecting group types. The compounds were dissolved in toluene and placed in thick walled flasks, sealed and heated to 150 °C in the presence of NIS. The second set of reaction
conditions were performed on the \( N \)-acetyl and \( N \)-BOC protected compounds in 1,2-DCE at 83 °C. In each case the expected products, iodoalkylidenes, (Scheme 39) were not obtained. The products were unidentifiable.

**Scheme 39: Attempted \( N \)-Iodosuccinimide Mediated Ring Expansion**

\[
\text{NHR} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{i-Pr} \quad \text{i-Pr} \\
\xrightarrow{\text{NIS heat}}
\text{NHR} \quad \begin{array}{c}
\text{I} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{i-Pr} \\
\begin{array}{c}
28a \quad R=\text{BOC} \\
46 \quad R=\text{Ac} \\
48 \quad R=\text{Bn}
\end{array}
\]

\[
\begin{array}{c}
28i \quad R=\text{BOC} \\
46i \quad R=\text{Ac} \\
48i \quad R=\text{Bn}
\end{array}
\]

**2.6. \( N \)-Chlorosuccinimide Mediated Ring Expansion**

The \( N \)-chlorosuccinimide ring expansions were attempted on 28a, 46 and 48 (Scheme 40). The NCS reaction with 28a was observed to cleave an isopropyl group and form dione 72 in 51% yield with alkyne still intact. The same result was observed for the reaction of 46 forming a 77% yield of 71. Unidentifiable products were obtained from reaction of 48. This type of rearrangement has been reported in the past for iodide mediated ring expansions (Scheme 41). The proposed mechanism is thought to proceed by the squarate hydroxyl group coordinating to the halide (structure B) followed by the loss of that hydroxyl moiety leaving a carbocationic intermediate C. Stabilization through the
resonance contribution of the alkoxy “trans” from the hydroxyl group could then allow the alkyl group on the alkoxy to be more easily removed. Removal of the alkyl group is likely to occur by halide attack thus forming the carbonyl and rearranged cyclobutenone \( D \).\(^{47}\) It is reasonable that the analogous reaction could occur using NCS. The NCS mediated ring expansions were not further examined using other \( N \)-BOC (28b-28e) protected derivatives.

**Scheme 40: Attempted \( N \)-Chlorosuccinimide Mediated Ring Expansion**

![Scheme 40](image)

**Scheme 41: Halide Mediated Cyclobutenone Rearrangement**

![Scheme 41](image)
3. Conclusions

These attempted indolization and ring expansion reactions were not further examined since the desired products were not obtained. The copper acetate catalyzed indolization of the N-acetyl derivative led to the preparation of novel 2-substituted indole. This methodology may be used in the future to prepare several other novel 2-substituted indoles. In the Cul mediated reactions with N-benzyl the project was dropped since the starting material was difficult to synthesize.
Part III

Synthesis of Novel Indoloquinones

1. Introduction

Indoloquinones are the core structure of many natural products including the mitosenes, isobatzellins, kinamycins and murrayaquinones. Many of these compounds are known to exhibit antitumor, antibacterial, antibiotic, antileukemia, antifungal, and myocardial contraction activity. For example, mitomycin C (73) exhibits both antitumor and antibiotic activity, isobatzellin A (74) exhibits antileukemia and moderate antifungal activities and murrayaquinone A (75) has been shown to induce myocardial contractions. Kinamycin D (76) is strongly active against Gram-positive bacteria and less active against Gram-negative bacteria.

Figure 3A: Indoloquinone Containing Natural Products
Indoloquinones 79 and 82 have been isolated from mid-intestinal gland of muricid gastropod *Drupella fragum* collected off the Japanese coast. These two compounds are shown to exhibit moderate antimicrobial activity against several bacterial strains. Compounds 79 and 82 were synthesized for structural confirmation. Isovanillin 77 was used to synthesize 79 in 7 steps. 77 was nitrated in the 2-position and the resulting hydroxybenzaldehyde 77a was acetylated 77b. The aldehyde was then alkylated with nitromethane followed by dehydration to yield a dinitrostyrene followed by reductive indolization led to indole 78. Deprotection and oxidation of 78 with salcomine under an atmosphere of oxygen gave indoloquinone 79 with a 6% overall yield. Indoloquinone 82 was synthesized in seven steps from 2,3-dimethoxybenzaldehyde 80 in a similar fashion in 12% overall yield (Scheme 42).56
Scheme 42: Existing Synthesis of *Drupella fragum* Indoloquinones 79 and 82

1. $\text{CHO} \xrightarrow{\text{NO}_2\text{BF}_4, \text{CH}_3\text{NO}_2, \text{CH}_2\text{Cl}_2, -40 \degree C} \text{CHO} \xrightarrow{\text{NaOAc, Ac}_2\text{O, 60} \degree \text{C}} \text{CHO}$

2. $\text{CHO} \xrightarrow{\text{KHMD}S, \text{CH}_3\text{NO}_2, \text{THF, -78} \degree \text{C-rt}} \text{CHO}$

3. $\text{CHO} \xrightarrow{1) \text{MsCl, CH}_2\text{Cl}_2, 0 \degree \text{C-rt}} \xrightarrow{2) \text{Fe, SiO}_2, \text{AcOH, PhCH}_3, 90 \degree \text{C}}$ 29% two steps

4. $\text{CHO} \xrightarrow{1) \text{NaOH, Na}_2\text{S}_{2}\text{O}_4, \text{DMF, 5} \degree \text{C}} \xrightarrow{2) \text{O}_2, \text{salcomine, rt}}$ 60%

5. $\text{CHO} \xrightarrow{\text{CHO}} \text{CHO}$
2. Results and Discussion

We envisioned that the synthesis of indoles using aliphatic aminoalkynes (83 and 87) and a squarate derivative (27). The butyne starting materials were synthesized according to literature procedures.\textsuperscript{57,58} Alkylation of 27 with 83 and alkylation of 87 was obtained in excellent yield (85%). Cyclobutenone 89 was produced in 62% yield along with a number of inseparable products, probably rotomers of the carbamate (Scheme 43). As we observed previously addition of the squarate derivatives was the most consistent method for alkylation.

Scheme 43: Alkylation of 27 with 83 and 87

\[ \text{R' RN} \quad 83 \quad \text{R} = \text{Bn, R'} = \text{H} \\
87 \quad \text{R} = \text{Bn, R'} = \text{Boc} \]

\[ 1) \text{n-BuLi, THF} \quad 2) \quad 27 \text{, THF} \]

Notes: a) -40 °C b) -78 °C

Upon thermal ring expansion of 88 and subsequent purification we were surprised to discover we had synthesized a novel 2,3-dihydroindoloquinone 91 in 51% yield (Scheme 44). During the separation the crude material changed color from yellow to green and finally to blue. Several other ring expansion conditions were attempted using xylenes (138 °C) and 1,2-DCE (83 °C). Reaction in xylenes led to faster conversion to 88 than compared to toluene but did not offer clean conversion to the indoloquinone (91). No reaction was observed using 1,2-DCE (83 °C) after 24 hours.
The proposed mechanism of the ring expansion, cyclization and oxidation is depicted in Scheme 45. The mechanism probably proceeds through the electrocyclic ring opening of 88 to give ketene 88a followed by the 6-endo-dig cyclization forming intermediate 88b. Subsequent hydrogen atom abstraction followed to give the diradical 88c and later 1,4-quinone formation (88d). The next step probably was a Michael addition of the amine to the quinone followed by proton shift and tautomerization forming the hydroquinone 90. Chromatography on silica gel probably caused the oxidation to indoloquinone 91.
Scheme 45: Proposed Mechanism for the Tandem Expansion/Cyclization of 89

Scheme 45 shows the proposed mechanism for the tandem expansion/cyclization of 89. The process involves several intermediates, denoted as 88, 88a, 88b, 88c, 88d, 88e, 88f, 90, and 91, which illustrate the stepwise addition and cyclization reactions leading to the final product.
Ammonium formate in the presence of Pd/C in refluxing MeOH has been reported to cleave the benzyl protecting groups.\textsuperscript{59} Compound 91 was subjected to these reaction conditions but 93 was formed in a disappointing 28% yield (Scheme 46).

**Scheme 46: Debenzylation of 91**

\[
\begin{align*}
\text{N} & \text{O} \\
\text{O} & \\
\text{Bn} & \\
\text{O} & \\
\text{i-Pr} & \\
\text{O} & \\
\text{i-Pr} & \\
\text{N} & \text{O} \\
\text{O} & \\
\text{H} & \\
\text{O} & \\
\text{i-Pr} & \\
\text{O} & \\
\text{i-Pr} & \\
\text{HCO}_2\text{NH}_4 \cdot 5\text{H}_2\text{O}, \text{Pd/C} & \\
\text{MeOH, reflux} & \\
91 & \rightarrow 93 (28\%) \\
\end{align*}
\]

DDQ has been used to oxidize dihydropyrroles to pyrroles\textsuperscript{60} and dihydroindoles to indoles\textsuperscript{61}. Compound 94 was produced in 65% yield via DDQ oxidation (Scheme 47).

**Scheme 47: DDQ Oxidation of 91 to 94**

\[
\begin{align*}
\text{N} & \text{O} \\
\text{O} & \\
\text{Bn} & \\
\text{O} & \\
\text{i-Pr} & \\
\text{O} & \\
\text{i-Pr} & \\
\text{DDQ, PhH} & \\
\text{rt-reflux} & \\
91 & \rightarrow 94 (65\%) \\
\end{align*}
\]

A shorter synthesis of 79 was envisioned using a ring expansion methodology. The proposed synthetic steps are outlined in Scheme 48.
Scheme 48: Proposed Route for the Synthesis of 79

Scheme 49: Ring Expansion of 89 to Quinone 92

Ring expansion of 89 is somewhat problematic in toluene affording a number of inseparable products. However the ring expansion was cleaner in 1,2-DCE in a sealed tube at 100 °C giving 92 in 48% yield (Scheme 49).

Scheme 50: Quinone 92 was deprotected with TFA and produced indoloquinone 91 in 51% yield (Scheme 50).
Scheme 50: Acidic Deprotection of 92 to 91

Future work should involve the synthesis of differently substituted alkynes to give 5 and 6 membered rings (Scheme 51).

Scheme 51: Proposed Future Research with Butyne Derivatives
3. Conclusions

In conclusion a novel route to indoloquinones has been discovered and may lead to the synthesis of a natural product, as well as several novel indoloquinones.
Part IV

Experimental

General Procedures. All NMR spectra were determined in CDCl₃ at 600 MHz (¹H NMR) and 150 MHz (¹³C NMR) unless otherwise stated. The chemical shifts are expressed in δ values relative to Me₄Si (0.0, ¹H and ¹³C) or CDCl₃ (77.0, ¹³C) internal standards. ¹H-¹H coupling constants are reported as calculated from spectra; thus, a slight difference between 𝐽_{a,b} and 𝐽_{b,a} is usually obtained. Results of APT (attached proton test) and DEPT-¹³C NMR experiments are shown in parentheses where, relative to CDCl₃, (-) denotes CH₃ or CH and (+) denotes CH₂ or C. For ¹H NMR, the assignments are: q = quartet, t = triplet, d = doublet, s = singlet, br = broad, and m = multiplet. Multiplet refers to unresolved resonances from one or more protons having intractable ¹H-¹H coupling constants.

Tetrahydrofuran (THF), toluene, dichloromethane, triethylamine, and diethyl ether were dried by passing through a steel column filled with activated alumina (8 x 14 mesh, Sorbent Technology) using argon pressure. Hexanes, EtOAc, and 1,2-dichloroethane (1,2-DCE) were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted first time used; all other reagents were obtained from commercial sources and used as received.

All reactions were performed in oven-dried glassware. n-BuLi concentrations were determined by titrating with either diphenyl acetic acid in THF or with tert-butanol, 1,10-phenanthroline in THF. Solvents were removed on a rotary evaporator at water aspirator pressure unless otherwise stated.
(4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester (37b). To a solution of 4-chloro-2-iodo-1-aminobenzene (36b) (1.44 g, 5.67 mmol) in THF (5 mL) sodium bis(trimethylsilyl)amide (NaHMDS) (1.0 M in THF, 12.5 ml, 12.5 mmol) was added via syringe over a 15 min period. A solution of BOC₂O (1.24 g, 5.67 mmol) in THF (5 mL) was added dropwise to the reaction mixture. The reaction mixture was then stirred at ambient temperature (24 h). The solvent was removed under reduced pressure and the residue was partitioned between HCl (aq., 0.1 M, 50 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was treated with sodium bicarbonate (saturated aq., 10 mL). The resulting aqueous phase was extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 95: 5) to give 37b (1.63 g, 4.60 mmol, 81%) as an off-white solid. mp 42-45 °C; ¹H NMR (270 MHz) δ 8.00 (d, 1H, J=8.9 Hz), 7.72 (d, 1H, J=2.4 Hz), 7.28 (dd, 1H, J=8.9 and 2.4 Hz), 6.79 (br s, 1H), 1.53 (s, 9H); ¹³C NMR (67.5 MHz) δ 152.3 (+), 137.7 (-), 137.6 (+), 129.1 (-), 128.4 (+), 120.4 (-), 88.2 (+), 81.4 (+), 28.2 (-); IR (CCl₄) 3400, 2980, 1738, 1157 cm⁻¹.

(2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester (37c). Reaction of 2-iodo-5-methoxyaniline (36c) (409 mg, 1.64 mmol), sodium bis(trimethylsilyl)amide (1.0 M in THF, 3.60 mL, 3.60 mmol), and Boc₂O (355 mg, 1.63 mmol) in THF, as described above for 37b (24 h), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) 37c (528 mg, 1.51 mmol, 92%) as
(2-Iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester (37d).

Reaction of 2-iodo-5-methyl-1-aminobenzene\textsuperscript{63} (36d) (897 mg, 3.84 mmol), sodium bis(trimethylsilyl)amide (1.0 M in THF, 4.2 ml, 8.4 mmol), and BOC\textsubscript{2}O (846 mg, 3.88 mmol) in THF, as described for 37b (24 h), gave after workup and chromatography (SiO\textsubscript{2}, hexanes:EtOAc, 8:2) 37d (1.122 g, 3.38 mmol, 88%) as an off-white solid. mp 79.5-82 °C; \textsuperscript{1}H NMR (270 MHz) \(\delta\) 7.91 (s, 1H), 7.59 (d, 1H, \(J=8.2\) Hz), 6.79 (br s, 1H), 6.60 (dd, 1H, \(J=1.6\) and 8.1 Hz), 2.31 (s, 3H), 1.54 (s, 9H); \textsuperscript{13}C NMR (67.5 MHz) \(\delta\) 152.5 (+), 139.4 (+), 138.4 (+), 138.3 (-), 125.7 (-), 120.6 (-), 84.6 (+), 80.9 (+), 28.3 (-), 21.3 (-); IR (CCl\textsubscript{4}) 3396, 2979, 2360, 1736, 1160 cm\textsuperscript{-1}.

(4-Chloro-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester (38b). A mixture of 37b (1.104 g, 3.12 mmol), bis(triphenylphosphine)palladium dichloride (22 mg, 0.031 mmol), copper iodide (7 mg, 0.037 mmol), and trimethylsilylethynyl (470 \(\mu\)L, 3.30 mmol) in triethylamine (20 mL) was stirred at ambient temperature (24 h). The reaction was diluted with water (50 mL) and the resulting biphasic mixture was extracted with diethyl ether
(3 x 50 mL). The combined organic layers were washed with NH₄OH (10% aq., 25 mL), dried (MgSO₄), filtered, and the solvent were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 95:5) to give 28b (924 mg, 2.84 mmol, 91%) as a yellow solid. mp 72-76 °C; ¹H NMR (270 MHz) δ 8.08 (1H, J=9.1 Hz), 7.34 (d, 1H, J=2.6 Hz), 7.31 (br s, 1H), 7.25 (dd, 1H, J=8.9 and 2.4 Hz), 1.53 (s, 9H), 0.29 (s, 9H); ¹³C NMR (67.5 MHz) δ 152.1 (+), 138.8 (+), 130.7 (-), 129.8 (-), 126.6 (+), 118.3 (-), 112.3 (+), 103.4 (+), 99.0 (+), 80.9 (+), 28.2 (-), -0.3 (-); IR (CCl₄) 3400, 2977, 2152, 1737, 1157 cm⁻¹.

(5-Methoxy-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (38c). Reaction of 37c (504 mg, 1.44 mmol), bis(triphenylphosphine)palladium dichloride (54 mg, 0.077 mmol), copper iodide (14 mg, 0.074 mmol), and trimethylsilylethylene (230 μL, 1.59 mmol) in triethylamine (30 mL), as described for 38b (ambient temperature, 24 h), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 95:5) 38c (360 mg, 1.16 mmol, 80%) off-white solid. mp 39-41 °C; ¹H NMR δ 7.78 (s, 1H), 7.39 (s, 1H), 7.26 (d, 1H, J=9.0 Hz), 6.49 (dd, 1H, J=7.8 and 1.8 Hz), 3.82 (s, 3H), 1.53 (s, 9H), 0.28 (s, 9H); ¹³C NMR δ 160.9 (+), 152.3 (+), 141.9 (+), 132.2 (-), 108.9 (-), 103.0 (+), 102.1 (-), 100.8 (+), 100.5 (+), 80.6 (+), 55.4 (-), 28.3 (-), -0.1 (-); IR (CCl₄) 3395, 2963, 2347, 2144, 1734, 1157 cm⁻¹.
(5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (38d). Reaction of 37d (450 mg, 1.36 mmol), bis(triphenylphosphine)palladium dichloride (48 mg, 0.068 mmol), copper iodide (16 mg, 0.084 mmol), and trimethylsilylthyne (200 μL, 1.42 mmol) in triethylamine (10 mL), as described for 38b (ambient temperature, 24 h), gave after workup and chromatography (SiO2, hexanes:EtOAc, 95:5) 38d (409 mg, 1.35 mmol, 100%) as a colorless oil. 1H NMR (270 MHz) δ 7.96 (s, 1H), 7.40 (br s, 1H), 7.15 (d, 1H, J=7.5 Hz), 6.75 (d, 1H, J=7.7 Hz), 2.34 (s, 3H), 1.53 (s, 9H), 0.28 (s, 9H); 13C NMR δ 152.4 (+), 140.5 (+), 140.1 (+), 131.0 (-), 122.8 (-), 117.7 (-), 108.1 (+), 101.3 (+), 100.8 (+), 80.5 (+), 28.3 (-), 22.0 (-), -0.1 (-); IR (CCl4) 3396, 2977, 2348, 2148, 1736, 1159 cm⁻¹.

(4-Trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester (38e). Reaction of (4-iodo-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester64 (37e) (1.96 g, 6.14 mmol), bis(triphenylphosphine)palladium dichloride (65 mg, 0.093 mmol), copper iodide (17 mg, 0.89 mmol), and trimethylsilylthyne (1.33 mL, 6.45 mmol) in triethylamine (20 mL), as described for 37b (ambient temperature, 24 h), gave after workup and chromatography (SiO2, hexanes:EtOAc, 1:1) 38e (1.78 g, 6.14 mmol, 100%) as a brown solid. mp 59-61 °C; 1H NMR (270 MHz) δ 9.39 (s, 1H), 8.24 (d, 1H, J=4.9 Hz), 7.21 (d, 1H, J=4.9 Hz), 7.12 (br s, 1H), 1.55 (s, 9H), 0.31 (s, 9H); 13C NMR (67.5 MHz) δ 151.8 (+), 142.9 (-), 139.9 (-), 135.8 (+), 124.2 (-), 118.2 (+), 106.9 (+), 97.6 (+), 81.4 (+), 28.1 (-), -0.4 (-); IR 3389, 2978, 2155, 1736, 1155 (CCl4) cm⁻¹.
(4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (26b). To a solution of 38b (924 mg, 2.85 mmol) in absolute ethanol:THF (1:1, 30 mL) was added a solution of NaOH (1 M, 3 mL) and the resulting reaction mixture was allowed to stir (ambient temperature, 2 h). The solvents were removed at reduced pressure and the residue was suspended in water (10 mL) and extracted with diethyl ether (3 x 50 mL). The organic layers were combined, dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes: EtOAc, 9:1) to give 26b (664 mg, 2.64 mmol, 92%) as an off-white solid. mp 61-63 °C; ¹H NMR (270 MHz) δ 8.13 (d, 1H, J=9.1 Hz), 7.39 (d, 1H, J=2.4 Hz), 7.29 (dd, 1H, J=9.1 and 2.6 Hz), 7.21 (br s, 1H), 3.52 (s, 1H), 1.53 (s, 9H); ¹³C NMR (67.5 MHz) δ 152.1 (+), 138.9 (+), 131.5 (-), 130.1 (-), 126.7 (+), 118.7 (-), 111.2 (+), 85.1 (+), 81.2 (+), 77.9 (+), 28.2 (-); IR (CCl₄) 3411, 3305, 2980, 2361, 1737, 1156 cm⁻¹.

(2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester (26c). To a solution of 38c (603 mg, 1.89 mmol) in methanol:THF:water (5:5:1, 11 mL) was added anhydrous potassium fluoride (334 mg, 5.75 mmol) and the resulting mixture was stirred (ambient temperature, 1 h). The reaction was diluted with water (50 mL) and extracted diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO₄), filtered, and the solvents were removed at reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 95:5) to give 26c (366 mg, 1.59 mmol, 84%) as a colorless solid. mp around ambient temperature. ¹H NMR (270 MHz) δ
7.83 (d, 1H, $J=2.4$ Hz), 7.32 (d, 1H, $J=8.5$ Hz), 7.29 (br s, 1H), 6.51 (dd, 1H, $J=8.7$ and 2.6 Hz), 3.83 (s, 3H), 3.42 (s, 1H), 1.53 (s, 9H); $^{13}$C NMR (67.5 MHz) $\delta 161.1$ (+), 152.3 (+), 141.8 (+), 133.1 (-), 109.1 (-), 102.4 (-), 101.8 (+), 82.8 (+), 80.9 (+), 79.5 (+), 55.4 (-), 28.3 (-); IR 3407, 3309, 2980, 2360, 1734, 1157 cm$^{-1}$.

(2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester (26d).

Reaction of 38d (400 mg, 1.32 mmol) with NaOH$^{65}$ (1 M aq., 4 mL) in absolute ethanol:THF (1:1, 20 mL), as described for 26b (ambient temp., 2 h), gave after workup and chromatography (SiO$_2$, hexanes: EtOAc, 9:1) 26d (241 mg, 1.05 mmol, 79%) as a yellow solid. mp 75-77 °C $^1$H NMR (270 MHz) $\delta$ 8.01 (s, 1H), 7.31 (d, 1H, $J=7.9$ Hz), 7.24 (br s, 1H), 6.78 (d, 1H, $J=7.9$), 3.4 (s, 1H), 2.35 (s, 3H), 1.53 (s, 9H); $^{13}$C NMR (67.5 MHz) $\delta$ 152.4 (+), 140.7 (+), 140.1 (+), 131.9 (-), 122.9 (-), 117.9 (-), 106.9 (+), 83.4 (+), 80.7 (+), 79.5 (+), 28.3 (-), 21.9 (-); IR (CCl$_4$) 3408, 3309, 2978, 2926, 2347, 1735, 1157 cm$^{-1}$.

Alternative Procedure for: (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester (26d).

Reaction of 38d (389 mg, 1.29 mmol) with anhydrous fluoride dihydrate (226 mg, 3.89 mmol) in methanol:THF (1:1, 20 mL), as described for 26d (ambient temperature, 1 h), gave after workup and chromatography (SiO$_2$, hexanes: EtOAc, 9:1) (217 mg, 0.94 mmol, 73%) a yellow solid.

(4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester (26e). Reaction of 38e (1.78 g, 6.14 mmol) with potassium fluoride dihydrate (1.72 g, 18.3 mmol)
in methanol:THF (1:1, 15 mL), as described for 26c (ambient temperature, 20 min), gave after workup and chromatography (SiO₂, hexanes: EtOAc, 1:1) 26e (1.32 g, 6.08 mmol, 99%) as a brownish solid. mp 77-80 °C; ¹H NMR (270 MHz) δ 9.40 (s, 1H), 8.26 (d, 1H J=4.9 Hz), 7.28 (d, 1H, J=5.1 Hz), 7.09 (br s, 1H), 3.69 (s, 1H), 1.57 (s, 9H); ¹³C NMR (67.5 MHz) δ 151.9 (+), 143.0 (-), 140.4 (-), 136.0 (+), 125.2 (-), 117.3 (+), 88.1 (+), 88.0 (+), 81.7 (+), 28.2 (-); IR (CCl₄) 3407, 3298, 2982, 2248, 1727, 1160 cm⁻¹.

Alternative Procedure for: (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester (26e).

Reaction of 38e (427 mg, 1.48 mmol) with NaOH (1 M aq., 5 mL) in absolute ethanol:THF (1:1, 20 mL), as described for 26c (ambient temp., 24 h), gave after workup and chromatography (SiO₂, hexanes: EtOAc, 7:3) (185 mg, 0.85 mmol, 61%) as a brownish solid.

[2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethylnyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (28a). To a -5 °C cold solution of (2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (26a) (155 mg, 0.71 mmol) in THF (10 mL) was slowly added n-BuLi (1.6 M in hexanes, 1.1 mL, 1.8 mmol) via syringe. After 15 min, a –5 °C cold solution 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (27) (141 mg, 0.71 mmol) in THF (10 mL) was added to the dilithiated compound via a cannula. The resulting reaction mixture was stirred (ambient temperature, 30 min) followed by the
addition of water (40 mL). The biphasic mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to afford 28a (189 mg, 0.45 mmol, 64%) as a brown oil and 26a (20 mg, 0.09 mmol). ³¹H NMR (270 MHz) δ 8.14 (d, 1H, J=8.3 Hz), 7.40 (dd, 1H, J=7.7 and 1.4 Hz), 7.32 (dt, 1H, J=8.7 and 1.6 Hz), 7.14 (br s, 1H), 6.95 (dt, 1H, J=7.5 and 1.0 Hz), 5.02 (heptet, 1H, J=6.1 Hz), 4.92 (heptet, 1H, J=6.1 Hz), 3.07 (br s, 1H), 1.53 (s, 9H), 1.48 (d, 3H, J=6.3 Hz), 1.47 (d, 3H, J=6.1 Hz) 1.33 (d, 3H, J=6.1 Hz), 1.32 (d, 3H, J=6.1 Hz); ¹³C NMR (67.5 MHz) δ 180.4 (+), 164.1 (+), 152.4 (+), 139.7 (+), 133.8 (+), 132.2 (-), 130.1 (-), 122.0 (-), 117.8 (-), 109.9 (+), 90.2 (+), 83.8 (+), 80.9 (+), 78.9 (+), 78.1 (-), 74.3 (-), 28.3 (-), 22.7 (-), 22.6 (-), 22.5 (-); IR (CCl₄) 3402, 2980, 2933, 1734, 1158 cm⁻¹.

Alternative Procedure for: [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (28a). 4-Ethynyl-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone69 (39) (272 mg, 1.21 mmol), bis(triphenylphosphine)palladium dichloride (45 mg, 0.063 mmol), copper iodide (238 mg, 1.25 mmol) were slurried in 30 mL NEt₃. 37a (394 mg, 1.23 mmol) was added after five minutes and the reaction was allowed to stir. After 24 hours the reaction was diluted with 50 mL water and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 20 mL 10% NH₄OH, dried (MgSO₄), filtered, and the solvents were removed under reduced
pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to afford 28a (189 mg, 0.35 mmol, 36%) as a brown oil and 37a (155 mg, 0.48 mmol, 61%).

[4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (28b). Reaction of 26b (250 mg, 0.99 mmol), n-BuLi (2.65 M in hexanes, 0.93 mL, 2.4 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (27) (198 mg, 1.00 mmol) in THF (20 mL total), as described for 28a (30 min), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2), 28b (349 mg, 0.77 mmol, 78%) as a yellow solid. mp 123-125 °C; ¹H NMR (270 MHz) δ 8.08 (d, 1H, J=8.9 Hz), 7.34 (d, 1H, J=2.4 Hz), 7.25 (dd, 1H, J=2.6 and 8.9 Hz), 7.15 (br s, 1H), 5.02 (heptet, 1H, J=6.1 Hz), 4.89 (heptet, 1H, J=6.1 Hz), 3.74 (br s, 1H), 1.53 (s, 9H), 1.48 (d, 3H, J=6.1 Hz), 1.47 (d, 3H, J=6.1 Hz); 13C NMR (67.5 MHz) δ 180.6 (+), 164.2 (+), 152.3 (+), 138.4 (+), 133.8 (+), 131.4 (-), 130.1 (-), 126.8 (+), 119.1 (-), 111.4 (+), 91.3 (+), 82.4 (+), 81.2 (+), 78.6 (+), 78.2 (-), 74.3 (-), 28.2 (-), 22.7 (-), 22.6 (-), 22.5 (-); IR (CCl₄) 3424, 2968, 2355, 1734, 1157 cm⁻¹.

[2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester (28c). Reaction of 26c (192 mg, 0.80 mmol), n-BuLi (1.4 M in hexanes, 1.43 mL, 2.01 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (27) (106 mg, 0.81 mmol) in THF
(25 mL total) as described for 28a (30 min), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) an inseparable mixture of 28c and 4-butyl-4-hydroxy-2,3-di(1-methylethoxy)-2-cyclobuten-1-one (215 mg, 4:1 ratio). Spectral data from the mixture: \(^1^H\) NMR (270 MHz) \(\delta\) 7.80 (d, 1H, \(J=2.2\) Hz), 7.28 (d, 1H, \(J=8.3\) Hz), 7.17 (br s, 1H), 6.50 (dd, 1H, \(J=8.5\) and 2.6 Hz), 5.02 (heptet, 1H, \(J=6.1\) Hz), 4.90 (heptet, 1H, \(J=6.3\) Hz), 3.82 (s, 3H), 3.21 (br s, 1H), 1.53 (s, 9H), 1.48 (d, 3H, \(J=6.3\) Hz), 1.46 (d, 3H, \(J=6.1\) Hz) 1.32 (d, 3H, \(J=6.1\) Hz), 1.31 (d, 3H, \(J=6.1\) Hz); \(^{13}\)C NMR (67.5 MHz) \(\delta\) 180.7 (+), 164.3 (+), 161.1 (+), 152.3 (+), 141.3 (+), 133.7 (+), 133.1 (-), 109.1 (-), 102.5 (-), 101.9 (+), 89.1 (-), 83.9 (+), 80.9 (+), 78.9 (+), 74.2 (-), 28.3 (-), 22.7 (-), 22.6 (-), 22.5 (-), 22.3 (-); IR (CCl₄) 3565, 2989, 2942, 1731, 1161 cm⁻¹.

**Alternative Procedure for: [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester (28c).** 4-Ethynyl-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone\(^{69}\) (39) (581 mg, 2.59 mmol), bis(triphenylphosphine)palladium dichloride (91 mg, 0.013 mmol), copper iodide (496 mg, 2.61 mmol) were slurried in 30 mL NEt₃. (2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester (37c) (912 mg, 2.61 mmol) was added after five minutes and the reaction was allowed to stir. After 20 hours the reaction was diluted with 50 mL water and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 20 mL 10% NH₃OH, dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂,
hexanes:EtOAc, 8:2) to afford 28c (747 mg, 1.68 mmol, 65%) as fluffy orange yellow solid. mp 38 – 42 °C. $^1$H NMR (270 MHz) $\delta$ 7.76 (d, 1H, $J = 2.4$ Hz), 7.26 (d, 1H, $J = 8.7$ Hz), 6.48 (dd, 1H, $J = 8.7$ and 2.6 Hz), 5.03 (heptet, 1H, $J = 6.1$ Hz), 4.88 (heptet, 1H, $J = 6.1$ Hz), 3.94 (br. s, 1H), 3.82 (s, 3H), 1.53 (s, 9H), 1.47 (overlapping d, 3H, $J = 6.2$ Hz), 1.46 (overlapping d, 3H, $J = 6.1$ Hz), 1.29 (d, 6H, $J = 6.1$ Hz); $^{13}$C NMR (67.5 MHz) $\delta$ 181.3 (+), 164.8 (+), 160.8 (+), 152.2 (+), 141.1 (+), 133.3 (+), 132.9 (-), 108.9 (-), 102.5 (-), 101.9 (+), 89.1 (+), 83.6 (+), 80.7 (+), 78.6 (+), 77.8 (-), 73.9 (-), 55.1 (-), 28.1 (-), 22.5 (-), 22.4 (-), 22.3 (-); IR (neat) 3398 (br.), 2979, 2213, 1774, 1730 cm$^{-1}$.

[2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester (28d). Reaction of 11c (241 mg, 1.05 mmol), n-BuLi (1.6 M in hexanes, 1.64 mL, 2.62 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (27) (207 mg, 1.04 mmol) in THF (30 mL total), as described for 28a (30 min), gave after workup and chromatography (SiO$_2$, hexanes:EtOAc, 8:2) 28d (222 mg, 0.52 mmol, 50%) as a yellow oil and 26c (70 mg, 0.30 mmol). $^1$H NMR (270 MHz) $\delta$ 7.98 (s, 1H), 7.26 (d, 1H, $J=7.9$ Hz), 7.12 (br s, 1H), 6.77 (d, 1H, $J=7.9$ Hz), 5.02 (heptet, 1H, $J=6.1$ Hz), 4.90 (heptet, 1H, $J=6.1$ Hz), 3.16 (br s, 1H), 2.34 (s, 3H), 1.53 (s, 9H), 1.48 (d, 3H, $J=6.3$ Hz), 1.46 (d, 3H, $J=6.1$ Hz) 1.32 (d, 3H, $J=6.1$ Hz), 1.31 (d, 3H, $J=6.1$ Hz); $^{13}$C NMR (67.5 MHz) $\delta$ 180.3 (+), 164.1 (+), 152.4 (+), 140.9 (+), 139.6 (+), 133.9 (+), 131.9 (-), 123.0 (-), 118.3 (-), 106.9 (+), 89.6 (+), 84.1 (+),
80.8 (+), 78.9 (+), 78.0 (-), 74.3 (-), 28.3 (-), 22.7 (-), 22.6 (-), 22.5 (-), 21.9 (-); IR (CCl4) 3424, 2978, 1731, 1637, 1161 cm\(^{-1}\).

**[4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethylnyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester (28e).** Reaction of 26e (1.05 g, 4.81 mmol), n-BuLi (2.89 M in hexanes, 4.16 mL, 12.04 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (27) (0.96 g, 4.83 mmol) in THF (40 mL total), as described for 28a, gave after workup and chromatography (SiO\(_2\), hexanes:EtOAc, 1:1), 28e (1.14 g, 2.74 mmol, 57%) as a brown oil. \(^1\)H NMR (270 MHz) \(\delta\) 9.40 (s, 1H), 8.24 (d, 1H, \(J=4.9\) Hz), 7.24 (d, 1H, \(J=4.9\) Hz), 6.99 (br s, 1H), 5.02 (heptet, 1H, \(J=6.1\) Hz), 4.91 (heptet, 1H, \(J=6.1\) Hz), 4.57 (br s, 1H), 1.53 (s, 9H), 1.47 (d, 3H, \(J=6.3\) Hz), 1.46 (d, 3H, \(J=6.1\) Hz) 1.32 (d, 3H, \(J=6.1\) Hz), 1.31 (d, 3H, \(J=6.1\) Hz); \(^13\)C NMR (67.5 MHz) \(\delta\) 180.0 (+), 164.0 (+), 151.8 (+), 142.3 (-), 139.9 (-), 139.8 (-), 135.7 (+), 133.8 (+), 125.3 (-), 118.0 (+), 95.5 (+), 81.6 (+), 80.5 (+), 78.5 (+), 78.1 (-), 78.0 (-), 74.3 (-), 74.2 (-), 28.1 (-), 22.6 (-), 22.5 (-), 22.4 (-); IR (CCl4) 3405 (br.), 2978, 2360, 1737, 1158 cm\(^{-1}\).

**[2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (33a).** A solution of 28a (325 mg, 0.78 mmol) in toluene (20 mL) was heated at reflux overnight. The reaction was cooled to ambient temperature and the solvent was removed under reduced pressure. The crude residue was purified by chromatography (SiO\(_2\), hexanes:EtOAc, 95:5) to give 33a (265 mg, 0.64 mmol, 82%) as an orange solid. mp 93-
96 °C; $^1$H NMR (270 MHz) $\delta$ 7.91 (dd, 1H, $J$=7.9 and 1.6 Hz), 7.80 (d, 1H, $J$=8.1 Hz), 7.44 (s, 1H), overlapping 7.40 (t, 1H, $J$=8.7 Hz), 7.13 (t, 1H, $J$=7.5 Hz), 6.54 (br s, 1H), 5.59 (m, 2H), 1.51 (s, 9H), 1.40 (d, 6H, $J$=6.3 Hz), 1.37 (d, 6H, $J$=6.1 Hz); $^{13}$C NMR (67.5 MHz) $\delta$ 185.9 (+), 184.4 (+), 152.8 (+), 151.9 (+), 149.4 (+), 137.8 (+), 131.7 (-), 131.5 (-), 130.8 (-), 127.3 (+), 124.2 (+), 123.4 (-), 122.2 (-), 80.9 (+), 74.9 (-), 74.8 (-), 28.2 (-), 22.9 (-), 22.6 (-); IR (CDCl$_3$) 3326 (br), 2980, 2933, 1733, 1156 cm$^{-1}$.

[4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (33b). Reaction of 28b (452 mg, 1.00 mmol) in toluene (20 mL), as described for 33a, gave after workup and chromatography (SiO$_2$, hexanes:EtOAc, 8:2) 33b (307 mg, 0.68 mmol, 68%) as a yellow solid. mp 57-62 °C; $^1$H NMR (270 MHz) $\delta$ 7.93 (d, 1H, $J$=2.4 Hz), 7.79 (d, 1H, $J$=8.5 Hz), 7.34 (dd, 1H, $J$=8.7 and 2.4 Hz), 7.32 (s, 1H), 6.48 (br s, 1H), 5.59 (m, 2H), 1.51 (s, 9H), 1.40 (d, 6H, $J$=5.5 Hz), 1.38 (d, 6H, $J$=5.9 Hz); $^{13}$C NMR $\delta$ 185.4 (+), 184.0 (+), 152.7 (+), 152.6 (+), 149.8 (+), 136.3 (+), 131.2 (-), 131.0 (-), 128.9 (+), 128.7 (-), 128.5 (+), 81.3 (+), 75.2 (-), 75.1 (-), 65.8 (+), 28.2 (-), 23.0 (-), 23.0 (-), 15.2 (-); IR (CDCl$_3$) 3149, 2982, 2254, 1727, 1160 cm$^{-1}$.

[2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxy-phenyl]-carbamic acid 1,1-dimethylethyl ester (33c). Reaction of a 4:1 mixture of 28c:4-butyl-4-hydroxy-2,3-di(1-methylethoxy)-2-cyclobuten-1-one (215 mg) in toluene (20 mL), as described for 33a (110 °C, 18h), gave after was
chromatography (SiO₂, hexanes:EtOAc, 8:2) 33c (84 mg, 0.19 mmol, 39% from 28c) as an orange-yellow solid. mp 99-102 °C; ¹H NMR (270 MHz) δ 8.15 (d, 1H, J=9.0 Hz), 7.48 (br s, 1H), 7.38 (s, 1H), 6.79 (s, 2H), 6.68 (dd, 1H, J=8.4 and 2.4 Hz), 5.53 (m, 2H), 3.85 (s, 3H), 1.52 (s, 9H), 1.39 (d, 6H, J=6.0 Hz), 1.38 (d, 6H, J=6.0 Hz); ¹³C NMR δ 186.8 (+), 185.0 (+), 162.9 (+), 152.5 (+), 151.4 (+), 148.4 (+), 140.3 (+), 133.8 (-), 130.5 (-), 124.5 (+), 116.0 (+), 110.1 (-), 106.3 (+), 81.1 (+), 74.8 (-), 74.7 (-), 55.4 (-), 28.2 (+), 22.9 (+); IR (CCl₄) 3445, 2980, 2933, 1733, 1670, 1156 cm⁻¹.

[2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester (33d). Reaction of 28d (59 mg, 0.14 mmol) in toluene (20 mL), as described for 33a (reflux, overnight), gave after chromatography (SiO₂, hexanes:EtOAc, 8:2) 33d (49 mg, 0.11 mmol, 83%) as a colorless oil. ¹H NMR (270 MHz) δ 7.89 (d, 1H, J=8.1 Hz), 7.65 (s, 1H), 7.42 (s, 1H), 6.95 (d, 1H, J=7.1 Hz), 6.56 (br s, 1H), 5.57 (m, 2H), 2.37 (s, 3H), 1.51 (s, 9H), 1.40 (d, 6H, J=6.1 Hz), 1.37 (d, 6H, J=6.1 Hz); ¹³C NMR (67.5MHz) δ 186.3 (+), 184.7 (+), 152.8 (+), 151.8 (+), 149.1 (+), 142.8 (+), 137.9 (+), 131.8 (-), 130.8 (-), 126.4 (+), 124.5 (-), 122.5 (-), 121.3 (+), 80.9 (+), 74.9 (-), 74.8 (-), 29.7 (+), 28.3 (-), 23.0 (-), 21.8 (-); IR (CCl₄) 3437, 2980, 2933, 1733, 1672, 1157 cm⁻¹.

[4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyridinyl]-carbamic acid 1,1-dimethylethyl ester (33e). Reaction of 28e (107 mg, 0.26
mmol) in refluxing 1,2-dichloroethane70 (20 mL) 18 h. The reaction was cooled to room temperature and the solvent was removed. The resulting residue was chromatographed (SiO2, hexanes:EtOAc, 6:4) 33e (83 mg, 0.20 mmol, 78%) as a brown solid. mp 117-119 °C; 1H NMR δ 8.99 (s, 1H), 8.40 (d, 1H, J=5.3 Hz), 7.66 (d, 1H, J=5.2 Hz), 7.30 (s, 1H), 6.45 (br s, 1H), 5.61 (m, 2H), 1.51 (s, 9H), 1.41 (d, 6H, J=6.3 Hz), 1.38 (d, 6H, J=6.3 Hz); 13C NMR δ 184.5 (+), 183.6 (+), 153.1 (+), 152.6 (+), 150.8 (+), 144.8 (-), 144.3 (-), 133.1 (+), 132.3 (+), 130.7 (+), 127.3 (-), 124.2 (-), 81.6 (+), 75.5 (-), 75.4 (-), 28.1 (-), 23.0 (-); IR (CCl4) 3000, 2960, 1740, 1690, 1160 cm⁻¹.

2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-one (34a). A solution of 33a (169 mg, 0.41 mmol) in EtOAc:HCl67 (1:1, 3 M aq. HCl, 20 mL) was stirred at ambient temperature (6 d). The solvents were removed under reduced pressure and the resulting residue was suspended in water (20 mL) and extracted with diethyl ether (100 mL). The organic layers were washed with NaHCO3 (aq. saturated 25 mL), dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO2, hexanes:EtOAc, 8:2) to give 34a (112 mg, 0.27 mmol, 66%) as a yellow-orange solid. mp 59-61 °C; 1H NMR (270 MHz) δ 8.05 (d, 1H, J=8.3 Hz), 7.79 (s, 1H), 7.71 (dd, 1H, J=7.9 and 1.4 Hz), 7.62 (dt, 1H, J=7.1 and 1.4 Hz), 7.42 (dt, 1H, J=8.1 and 1.2 Hz), 5.68 (heptet, 1H, J=6.3 Hz), 5.26 (heptet, 1H, J=6.1 Hz), 1.50 (d, 6H, J=6.1 Hz), 1.35 (d, 6H, J=6.1 Hz); 13C NMR (67.5 MHz) δ 187.2 (+), 158.0 (+), 156.8 (+), 149.2 (+), 138.2 (+), 130.6 (-), 129.8 (-), 129.7 (-), 127.7 (+), 126.8
(-), 126.3 (-), 123.7 (+), 76.5 (-), 73.8 (-), 22.9 (-), 22.8 (-); IR (CCl₄) 3436, 2978, 1695, 1102 cm⁻¹.

**Alternative procedure for: 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-one (34a).** A solution of 33a (566 mg, 1.36 mmol) in CH₂Cl₂ (20 mL) was treated with 2.5 mL TFA¹⁶⁸ (trifluoroacetic acid) at 0 °C for 30 minutes. The reaction was then warmed to 50 °C for 3h. The reaction was cooled to room temperature and the solvents were removed under reduced pressure. The resulting residue was neutralized with 30 mL aqueous saturated NaHCO₃ and extracted with 3X 30 mL portions of CH₂Cl₂. The organic layer was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to give 33a (298 mg, 1.00 mmol, 74%) as a yellow-orange solid.

**7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-one (34b).** Reaction of 33b (163 mg, 0.44 mmol) in EtOAc:HCl⁶⁷ (1:1, 3 M aq. HCl, 30 mL), as described for 34a (ambient temperature, 3 d), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2), 34b (71 mg, 0.24 mmol, 54%) as an orange solid. mp 104-106 °C; ¹H NMR (270 MHz) δ 7.99 (d, 1H, J=8.9 Hz), 7.69 (s, 1H), 7.68 (s, 1H) overlapping 7.61 (d, 1H, J=2.3 Hz), 7.55 (dd, 1H, J=8.7 and 2.3 Hz), 5.66 (heptet, 1H, J=6.1 Hz), 5.28 (heptet, 1H, J=6.1 Hz), 1.51 (d, 6H, J=6.3 Hz), 1.36 (d, 6H, J=6.3 Hz); ¹³C NMR (67.5 MHz) δ 186.5 (+), 158.5 (+), 156.7 (+), 147.5 (+), 138.4 (+), 132.4 (+), 131.0 (-), 128.6 (-), 128.5 (-), 125.2
2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-one (34c). Reaction of 33c (154 mg, 0.35 mmol) in EtOAc:HCl\textsuperscript{67} (4:3, 3 M aq. HCl, 35 mL), as described for 34a (ambient temperature, 2 d), gave after workup and chromatography (SiO\textsubscript{2}, hexanes:EtOAc, 8:2) \textbf{34c} (88 mg, 0.27 mmol, 78\%) as a yellow oil. \textsuperscript{1}H NMR (270 MHz) \(\delta\) 7.73 (s, 1H), 7.60 (d, 1H, \(J=8.7\) Hz), 7.48 (d, 1H, \(J=2.6\) Hz), 7.05 (dd, 1H, \(J=8.7\) and 2.6 Hz), 5.62 (heptet, 1H, \(J=6.1\) Hz), 5.23 (heptet, 1H, \(J=6.1\) Hz), 3.92 (s, 3H), 1.49 (d, 6H, \(J=6.1\) Hz), 1.34 (d, 6H, \(J=6.1\) Hz); \textsuperscript{13}C NMR (67.5 MHz) \(\delta\) 187.6 (+), 161.6 (+), 159.2 (+), 156.1 (+), 151.0 (+), 137.1 (+), 130.6 (-), 126.1 (-), 121.9 (+), 121.2 (+), 117.9 (-), 109.9 (-), 74.8 (-), 73.7 (-), 55.5 (-), 22.8 (-), 22.7 (-); IR (CCl\textsubscript{4}) 2980, 2932, 2359, 1701, 1108 cm\textsuperscript{-1}.

2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-one (34d). Reaction of 33d (185 mg, 0.43 mmol) in EtOAc:HCl\textsuperscript{67} (3:2, 3 M aq. HCl, 25 mL), as described for 34a (ambient temperature, 2 d), gave after workup and chromatography (SiO\textsubscript{2}, hexanes:EtOAc, 8:2) \textbf{34d} (94 mg, 0.30 mmol, 70 \%) as a yellow-orange solid. mp 78-80 °C; \textsuperscript{1}H NMR (270 MHz) \(\delta\) 7.85 (s, 1H), 7.75 (s, 1H), 7.60 (d, 1H, \(J=8.1\) Hz), 7.26 (dd, 1H, \(J=7.5\) and 1.4 Hz), 5.67 (heptet, 1H, \(J=6.1\) Hz), 5.22 (heptet, 1H, \(J=6.1\) Hz), 2.46 (s, 3H), 1.49 (d, 6H, \(J=6.1\) Hz), 1.34 (d, 6H, \(J=6.1\) Hz); \textsuperscript{13}C NMR (67.5 MHz) \(\delta\) 187.3 (+), 158.5 (+), 156.5 (+), 149.2 (+), 141.2 (+), 137.8 (+), 129.5 (-), 129.4 (-), 128.5 (-), 126.2 (-), 125.3 (+), 122.8 (-), 1101 cm\textsuperscript{-1}.  

76
(+) 74.9 (-), 73.7 (-), 22.9 (-), 22.7 (-), 21.7 (-); IR (CCl₄) 3000, 2950, 1715, 1645, 1155 cm⁻¹.

**2,3-Di(1-methylethoxy)-6-aza-cyclopenta[b]quinolin-1-one (34e).** To a 0 °C cold solution of 33e (273 mg, 0.66 mmol) in CH₂Cl₂ (15 mL) was slowly added trifluoroacetic acid (1.0 mL, 5.93 mmol). The reaction mixture was allowed to stir (0 °C, 4 h, then reflux, 1 h). The solvent was removed under reduced pressure and the residue was suspended in NaHCO₃ (aq. saturated, 10 mL). The suspension was extracted with CH₂Cl₂ (100 mL) and the combined organic layers were, dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 1:1) to give 34e (168 mg, 0.56 mmol, 86%) as an orange solid. mp 73-76 °C; ¹H NMR (270 MHz) δ 9.37 (s, 1H), 8.55 (d, 1H, J=5.3 Hz), 7.74 (s, 1H), 7.55 (d, 1H, J=5.2 Hz), 5.71 (heptet, 1H, J=6.1 Hz), 5.32 (heptet, 1H, J=6.1 Hz), 1.51 (d, 6H, J=6.1 Hz), 1.36 (d, 6H, J=6.1 Hz); ¹³C NMR δ 185.6 (+), 159.6 (+), 156.9 (+), 152.9 (-), 145.4 (-), 143.9 (+), 139.8 (+), 131.9 (+), 127.7 (+), 124.2 (-), 121.9 (-), 75.6 (-), 74.1 (-), 22.9 (-), 22.8 (-); IR (CHCl₃) 2985, 2348, 2254, 1704, 1094 cm⁻¹.

**2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-ol (35a).** To a 0 °C cold solution of 34a (96 mg, 0.32 mmol) in THF (10 mL) was added NaBH₄ (130 mg, 3.44 mmol) and the resulting mixture was allowed to stir (3 h). Methanol (1.55 mL, 35.51 mmol) was added and the mixture was diluted with water (20 mL) and
extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to afford 35a (81 mg, 0.27 mmol, 84%) as a pale yellow oil. ¹H NMR δ 7.93 (d, 1H, J=7.8), 7.78 (s, 1H), 7.53 (m, 2H), 7.32 (dt, 1H, J=1.2, 7.8 Hz), 5.29 (heptet, 1H, J=5.4 Hz), 5.13 (heptet, 1H, J=6.0 Hz), 5.02 (br s, 1H), 2.75 (br s, 1H), 1.36 (d, 3H, J=5.4 Hz), 1.34 (d, 3H, J=6.0 Hz) 1.33 (d, 3H, J=6.0 Hz), 1.31 (d, 3H, J=6.0 Hz); ¹³C NMR δ 159.8 (+), 151.5 (+), 148.2 (+), 133.8 (+), 131.1 (+), 128.7 (-), 128.5 (-), 128.1 (-), 127.9 (-), 126.4 (+), 124.8 (-), 72.9 (-), 72.3 (-), 68.7 (-), 22.91 (-), 22.90 (-), 22.64 (-), 22.61 (-); IR (CCl₄) 3277, 3061, 2979, 2935, 2360, 1317, 1104 cm⁻¹.

7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-ol (35b). Reaction of 34b (80 mg, 0.27 mmol) with NaBH₄ (106 mg, 2.80 mmol), and methanol (1.30 mL, 29.58 mmol) in THF (10 mL), as described for 35a (3 h), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) 35b (55 mg, 0.18 mmol, 68%) as a light yellow oil. ¹H NMR δ 7.83 (d, 1H, J=9.0 Hz), 7.58 (s, 1H), 7.51 (d, 1H, J=1.8 Hz), 7.47 (dd, 1H, J=8.4 and 2.4 Hz), 5.24 (heptet, 1H, J=6.0 Hz), 5.15 (heptet, 1H J=6.0 Hz), 5.01 (br s, 1H), 2.75 (br s, 1H), 1.40 (d, 3H, J=6.0 Hz), 1.36 (d, 3H, J=6.0 Hz), 1.35 (d, 3H, J=6.0 Hz), 1.34 (d, 3H, J=6.0 Hz); ¹³C NMR δ 160.3 (+), 152.2 (+), 146.8 (+), 133.8 (+), 132.2 (+), 130.4 (-), 130.1 (-), 129.6 (+), 127.3 (-), 127.2 (-), 126.9 (+), 73.4 (-), 72.7 (-), 68.8 (-), 23.17 (-), 23.15 (-), 22.87 (-), 22.83 (-); IR (CHCl₃) 3366 (br.), 2976, 1313, 1104.
2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-ol (35c). Reaction of 34c (61 mg, 0.19 mmol), NaBH₄ (80 mg, 2.11 mmol), and methanol (0.91 mL, 20.95 mmol) in THF (10 mL), as described for 35a (18h), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) 35c (43 mg, 0.13 mmol, 70%) as a yellow oil. $^1$H NMR (270 MHz) $\delta$ 7.78 (s, 1H), 7.56 (d, 1H, $J=8.9$ Hz), 7.40 (d, 1H, $J=2.4$ Hz), 7.03 (dd, 1H, $J=8.7$ and 2.6 Hz), 5.34 (heptet, 1H, $J=5.7$ Hz), 5.12 (heptet, 1H, $J=5.9$ Hz), 5.06 (d, 1H, $J=6.9$ Hz), 3.92 (s, 3H), 1.38 (m, 12H); $^{13}$C NMR (67.5 MHz) $\delta$ 160.2 (+), 159.9 (+), 151.1 (+), 149.7 (+), 133.9 (+), 128.8 (+), 127.9 (-), 120.9 (+), 116.6 (-), 107.9 (-), 72.9 (-), 72.3 (-), 68.6 (-), 55.4 (-), 22.9 (-), 22.6 (-); IR (CCl₄) 3412, 2977, 2931, 1105 cm$^{-1}$.

2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-ol (35d). Reaction of 34d (94 mg, 0.30 mmol), NaBH₄ (118 mg, 2.80 mmol), and methanol (1.44 mL, 33.2 mmol) in THF (10 mL), as described for 35a (18h), gave after workup and chromatography (SiO₂, hexanes: EtOAc, 8:2) 35d (66 mg, 0.21 mmol, 70%) as a faint yellow oil. $^1$H NMR $\delta$ 7.79 (s, 2H), 7.58 (d, 1H, $J=7.9$ Hz), 7.21 (d, 1H, $J=9.1$ Hz), 5.39 (heptet, 1H, $J=6.1$ Hz), 5.15, (heptet, 1H, $J=6.1$ Hz), 5.04 (d, $J=5.1$ Hz), 2.51 (s, 3H), 1.38 (m, 12H); $^{13}$C NMR $\delta$ 159.6 (+), 151.4 (+), 148.1 (+), 138.8 (+), 133.7 (+), 130.2 (+), 127.9 (-), 127.7 (-), 127.5 (-), 126.6 (-), 124.1 (+), 72.8 (-), 72.2 (-), 68.5 (-), 22.9 (-), 22.6 (-), 21.6 (-); IR (CCl₄) 3400, 2978, 2933, 1105 cm$^{-1}$.
2,3-Di(1-methylethoxy)-6-azacyclopenta[b]quinolin-1-ol (35e). To a 0 °C cold solution of 34e (414 mg, 3.36 mmol) in THF:MeOH (1:1, 10 mL) was added NaBH₄ (110 mg, 2.91 mmol). The reaction was stirred for 10 min at 0 °C and subsequently quenched with water (20 mL). The mixture was quickly extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and the solvents were removed under reduced pressure. The residue was purified by chromatography (SiO₂, hexanes:EtOAc, 3:7) to give 35e (212 mg, 0.71 mmol, 51%) as a white solid which quickly turned yellow. Tentative NMR assignments from a rapidly decomposing compound. ¹H NMR (270 MHz) δ 9.25 (s, 1H), 8.39 (d, 1H, J=5.3 Hz), 7.77 (s, 1H), 7.46 (d, 1H, J=5.5 Hz), 5.25 (overlapping heptet, 2H), 5.07 (s, 1H), 1.46-1.32 (m, 12H); ¹³C NMR (67.5 MHz) δ 161.5 (+), 153.6 (+), 151.6 (-), 143.4 (+), 142.2 (-), 136.3 (+), 133.5 (+), 130.3 (+), 126.1 (-), 120.7 (-), 73.4 (-), 72.5 (-), 68.3 (-), 28.2 (-), 22.9 (-), 22.6 (-).

[2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethylethyl ester (41). Reaction of 26a (406 mg, 1.87 mmol), n-BuLi (1.6 M in hexanes, 2.90 mL, 4.67 mmol), and 3-methyl-4-(1-methylethoxy)-3-cyclobutene-1,2-dione⁶⁹ (40) (290 mg, 1.88 mmol) in THF (30 mL total), as described for 28a (30 min), gave after workup and chromatography (SiO₂, hexanes: EtOAc, 8:2) 41 (410 mg, 1.10 mmol, 48%) as a yellow solid and 26a (81 mg, 0.37 mmol, 59%). ¹H NMR (270 MHz) δ 8.11 (d, 1H, J=8.5 Hz), 7.33 (dt, 1H, J=1.6, 7.5 Hz), 7.21 (br s, 1H), 6.93 (dt, 1H, J=7.5 and 1.0 Hz), 5.11 (heptet, 1H, J=6.3 Hz), 4.24 (br s, 1H), 1.71 (s, 1H), 1.53 (s, 9H), 1.49 (d, 6H,
\( J = 6.3 \text{ Hz} \); \( ^{13}\text{C} \) NMR (67.5 MHz) \( \delta \) 187.6 (+), 180.1 (+), 152.5 (+), 139.7 (+), 132.1 (-), 130.1 (-), 124.3 (+), 122.1 (-), 118.0 (-), 110.0 (+), 90.1 (+), 84.8 (+), 83.2 (+), 80.9 (+), 78.5 (-), 28.2 (-), 22.9 (-), 22.6 (-), 6.5 (-); IR (CCl\(_4\)) 3410, 2980, 2380, 1735, 1157 cm\(^{-1}\).

**E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (42).** Reaction of 41 (310 mg, 0.83 mmol) in 1,2-dichloroethane (20 mL), as described for 33e (18h), gave after chromatography (SiO\(_2\), hexanes:EtOAc, 8:2) an inseparable mixture of E- and Z-42 (152 mg, 0.41 mmol, 8.3:1 ratio, 49%) as a yellow solid. mp 132-136 °C; \( ^{1}\text{H} \) NMR (270 MHz) \( \delta \) 8.05 (dd, 1H, \( J = 7.9 \) and 1.6 Hz), 7.76 (d, 1H, \( J = 8.3 \) Hz), 7.48 (s, 1H), 7.43 (dt, 1H, \( J = 7.7 \) and 1.6 Hz), 7.16 (t, 1H), 6.63 (br s, 1H), 5.73 (heptet, 1H, \( J = 6.1 \) Hz), 1.99 (s, 3H), 1.51 (s, 9H), 1.41 (d, 6H, \( J = 5.9 \) Hz); \( ^{13}\text{C} \) NMR \( \delta \) (150 MHz) 189.3 (+), 188.2 (+), 164.8 (+), 152.9 (+), 138.1 (+), 137.5 (+), 132.7 (-), 132.2 (-), 131.9 (-), 131.5 (-), 127.9 (+), 123.7 (-), 122.6 (-), 80.9 (+), 74.8 (-), 74.7 (-), 28.2 (-), 23.2 (-), 7.2 (-); IR (CCl\(_4\)) 3400, 2978, 2931, 2359, 1733, 1156 cm\(^{-1}\).

**2-(1-Methylethoxy)-3-methylcyclopenta[b]quinolin-1-one (43).** Reaction of 42 (141 mg, 0.39 mmol) in EtOAc:HCl (3:2, 3 M aq. HCl, 25 mL), was stirred at room temperature for 3h followed by heating at 60 °C for 1h. The solvents were removed under reduced pressure and the residue was diluted in 50 mL H\(_2\)O. The aqueous phase was extracted with 3X 50 mL of Et\(_2\)O, washed with 20 mL
saturated NaHCO₃, dried (MgSO₄) and chromatographed on silica gel (hexanes:EtOAc, 8:2) gave 43 (54 mg, 0.21 mmol, 56%) as a yellow-orange solid. mp 78-80 °C; ¹H NMR (270 MHz) δ 7.94 (d, 1H, J=8.3 Hz), 7.93 (s, 1H), 7.71 (d, 1H, J=8.3 Hz), 7.63 (t, 1H, J=7.1 Hz), 7.39 (t, 1H, J=7.5 Hz), 5.28 (heptet, 1H, J=6.1 Hz), 2.19 (s, 3H), 1.34 (d, 6H, J=6.1 Hz); ¹³C NMR δ 189.4 (+), 163.9 (+), 156.1 (+), 150.1 (+), 139.0 (+), 131.3 (-), 130.5 (-), 129.6 (-), 128.1 (-), 127.5 (+), 126.6 (-), 123.3 (+), 73.9 (-), 23.2 (-), 8.3 (-); IR (CCl₄) 2988, 2254, 1707, 1636, 1102 cm⁻¹.

2-(1-methylethoxy)-3-methylcyclopenta[b]quinolin-1-ol (44). Reaction of 43 (90 mg, 0.36 mmol), NaBH₄ (140 mg, 3.70 mmol), and methanol (1.7 mL, 39.1 mmol) in THF (10 mL), as described for 35a (3 h), gave after workup and chromatography (SiO₂, hexanes:EtOAc) 44 (73 mg, 0.29 mmol, 81%) as a yellow oil. Tentative NMR assignments from a rapidly decomposing compound: ¹H NMR δ 7.76 (d, 1H, J=8.4 Hz), 7.53 (dt, 1H, J=7.8 and 2.4 Hz), 7.24 (dt, 1H, J=8.4 and 1.8 Hz), 7.15 (dd, 1H, J=7.8 and 1.8 Hz), 6.99 (s, 1H), 5.01 (heptet, 1H, J=5.4 Hz), 4.97 (t, 1H, J=1.8 Hz), 1.91 (d, 3H, J=1.2 Hz), 1.46 (d, 3H, J=6.6 Hz), 1.30 (d, 3H, J=6.6 Hz); ¹³C NMR δ 167.3 (+), 164.7 (+), 147.7 (+), 132.1 (+), 128.8 (-), 128.3 (-), 127.5 (-), 127.4 (+), 126.3 (+), 124.1 (-), 115.8 (+), 72.7 (-), 69.6 (-), 23.3 (-), 23.1 (-), 6.9 (-).
N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide. (46)

N-(2-Ethynyl-phenyl)-acetamide\textsuperscript{71} (45) (330 mg, 2.07 mmol) was dissolved in 10 mL THF and cooled to -78 °C. \textit{n}-BuLi (1.6M in pentane, 3.40 mL, 5.41 mmol) was added slowly via syringe and stirred for 15 minutes at -78 °C. The dilithiated acetanilide was then transferred via cannula to a cold (-78 °C) 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (27) (415 mg, 2.09 mmol)/THF (10 mL) solution and allowed to stir for 30 minutes. The reaction was then allowed to warm to room temperature over 20 minutes. The reaction was quenched with 20 mL water and 5 mL saturated NH\textsubscript{4}Cl solution. The resulting biphasic mixture was extracted with (3 X 50 mL) diethyl ether. The organic layers were combined and washed with one portion of 30 mL saturated NaCl solution, dried (MgSO\textsubscript{4}), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO\textsubscript{2}, hexanes: EtOAc, 1:1) to give 46 (530 mg, 1.48 mmol, 71%) as a thick orange oil. \textsuperscript{1}H NMR (270 MHz) \(\delta\) 8.26-8.23 (m, 2H), 7.34-7.23 (m, 2H), 6.96 (t, 1H, \(J = 7.5\) Hz), 5.96 (br. s, 1H), 5.06 (heptet, 1H, \(J = 6.1\) Hz), 4.79 (heptet, 1H, \(J = 6.1\) Hz), 2.23 (s, 3H), 1.46 (d, 6H, \(J = 5.8\) Hz), \textsuperscript{13}C NMR (67.5 MHz) \(\delta\) 182.2 (+), 169.3 (+), 165.1 (+), 139.3 (+), 133.6 (+), 131.7 (-), 129.9 (-), 123.2 (-), 120.1 (-), 110.9 (+), 90.4 (+), 83.9 (+), 78.4 (-), 74.2 (-), 24.5 (-), 22.6 (-), 22.4 (-); IR (neat) 3312 (br.), 2980, 1773, 1673 cm\textsuperscript{-1}. 

4-Ethynyl-4-hydroxy-2,3-diisoproxy-cyclobut-2-enone (39) (391 mg, 1.74 mmol), bis(triphenylphosphine)palladium dichloride (62 mg, 0.088 mmol), copper iodide (336 mg, 1.76 mmol) were slurried in 30 mL NEt₃. (49) (912 mg, 2.612 mmol) was added after five minutes and the reaction was allowed to stir. After 24 hours the reaction was diluted with 50 mL water and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 20 mL 10% NH₄OH, dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 1:1) to give 46 (278 mg, 0.78 mmol, 45%) as a thick orange oil and 49 (118 mg, 0.45 mmol, 60%).

N-[2-(3,4-Diisoproxy-2,5-dioxo-cyclopent-3-enylidenemethyl)-phenyl]-acetamide (51).

N-[2-(1-Hydroxy-2,3-diisoproxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide (46) (390 mg, 1.09 mmol) was dissolved in 100 mL toluene and heated to reflux for 18 hours. The reaction was allowed to cool to room temperature and the solvent was removed. The residue was chromatographed on silica gel (hexanes:EtOAc 1:1) to give 51 (281 mg, 0.78 mmol, 72%) as an orange oil. ¹H NMR (270 MHz) δ 7.99 (br. s, 1H), 7.88 (d, 1H, J = 7.5 Hz), 7.82 (d, 1H, J = 8.1 Hz), 7.44 (t overlapping with s seen at 7.41, 1H, 7.1 Hz), 7.41 (s overlapping with t seen at 7.44, 1H), 5.54 (m, 2H), 2.22 (s, 3H), 1.36 (d, 6H, J =
3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. (70)

N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide (46) (116 mg, 0.323 mmol) was dissolved in 20 mL dry 1,2-dichloroethane. Cu(OAc)$_2$.H$_2$O (16 mg, 0.078 mmol) was added and the reaction was refluxed under nitrogen for 24h. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel yielding 70 (69 mg, 0.233 mmol, 72%) as a red orange oil. $^1$H NMR (270 MHz) $\delta$ 7.71 (d, 1H, $J = 8.1$ Hz), 7.53 (dt, 1H, $J = 1.4$, 7.5 Hz), 7.38 – 7.31 (m, 2H), 6.14 (s, 1H), 5.62 (heptet, 1H, $J = 6.1$ Hz), 2.43 (s, 3H), 1.51 (d, 6H, $J = 6.1$ Hz); $^{13}$C NMR $\delta$ 191.9 (+), 191.6 (+), 191.0 (+), 172.2 (+), 157.7 (+), 154.4 (+), 140.4 (+), 133.6 (-), 128.3 (-), 126.6 (-), 123.7 (-), 118.7 (+), 86.8 (-), 78.8 (-), 23.1 (-), 20.9 (-); IR (neat) 3321, 2981, 1703, 1667 cm$^{-1}$.

N-[2-(2-Isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide

(71). N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide (46) (164 mg, 0.46 mmol) was dissolved in 20 mL dry 1,2-dichloroethane. N-chlorosuccinimide (64 mg, 0.48 mmol) was added and the reaction was heated to reflux for 4 hours. After cooling to room temperature the
solvent was removed under reduced pressure. The residue was chromatographed on silica gel yielding 71 (105 mg, 0.35 mmol, 77%) as a yellow solid. mp 139-141 °C. $^1$H NMR $\delta$ 8.40 (d, 1H, J = 8.4 Hz), 7.95 (br. s, 1H), 7.46 – 7.42 (m, 2H), 7.08 (t, 1H, J = 7.2 Hz), 5.43 (heptet, 1H, J = 6.0 Hz), 2.27 (s, 3H), 1.54 (d, 6H, J = 6.6 Hz); $^{13}$C NMR $\delta$ 194.1 (+), 194.08 (+), 190.5 (+), 168.6 (+), 159.4 (+), 139.7 (+), 132.6 (-), 131.9 (-), 123.6 (-), 120.0 (-), 114.0 (+), 109.8 (+), 82.3 (+), 81.5 (-), 24.7 (-), 22.6 (-); IR (neat) 3325, 2991, 2191, 1784, 1766, 1676 cm$^{-1}$.

tert-butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)ethynyl)phenylcarbamate (72). [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (28a) (193 mg, 0.47 mmol) was dissolved in 20 mL dry 1,2-dichloroethane. N-chlorosuccinimide (71 mg, 0.53 mmol) was added and the reaction was heated to reflux for 4 hours. After cooling to room temperature the solvent was removed under reduced pressure. The residue was chromatographed on silica gel yielding 72 as an orange oil (85 mg, 0.24 mmol, 51%) $^1$H NMR $\delta$ (270 MHz) 8.22 (d, 1H, J = 8.3 Hz), 7.49-7.42 (m, 2H), 7.13 (br. s, 1H), 7.04 (dt, 1H, J = 1.0, 7.5 Hz), 5.46 (heptet, 1H, J = 6.3 Hz), 1.57 (d overlapping s at 1.55, 6H, J = 6.3 Hz), 1.55 (s overlapping d at 1.57, 9H); $^{13}$C NMR $\delta$ 194.7 (+), 194.5 (+), 189.9 (+), 159.9 (+), 152.0 (+), 140.1 (+), 132.4 (-), 122.5 (-), 118.2 (), 113.9 (-), 109.1 (+), 81.8 (+), 81.4 (+), 81.1 (-), 28.6 (-), 22.6 (-). IR (neat) 3411, 2981, 2934, 2184, 1786, 1730, 1089 cm$^{-1}$.
4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone (48).

Benzyl-(2-ethynyl-phenyl)-amine\textsuperscript{72} (47) (410 mg, 1.98 mmol) was dissolved in THF (10 mL) n-BuLi (2.82 M in hexanes, 0.74 mL, 2.09 mmol) was slowly added via syringe. After 20 min, a –5 °C cold solution 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (27) (394 mg, 1.99 mmol) in THF (10 mL) was added to the lithiated compound via cannula. The resulting reaction mixture was stirred (-5 °C, 30 min) followed by the addition of water and saturated NH\textsubscript{4}Cl solution (30 mL and 5 mL respectively). The biphasic mixture was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 30 mL brine, dried (MgSO\textsubscript{4}), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO\textsubscript{2}, hexanes:EtOAc, 8:2) to afford 48 (191 mg, 0.47 mmol, 24%) as a yellow brown solid. mp 134-135 °C and 47 (158 mg, 0.76 mmol, 39%). \textsuperscript{1}H NMR (270 MHz) δ 7.34-7.21 (m, 5H), 7.11 (dt, 1H, J = 1.5 and 7.1 Hz), 6.58 (t, 1H, J = 7.5 Hz), 6.49 (d, 1H, J = 8.3 Hz), 5.24 (br. s, 1H), 4.99 (heptet, 1H, J = 6.1 Hz), 4.83 (heptet, 1H, J = 5.9 Hz), 4.43 (s, 2H), 3.71 (br. s, 1H), 1.41 (d, 3H, J = 6.1 Hz), 1.36 (d, 3H, J = 6.2 Hz), 1.27 (overlapping d, 3H, J = 6.1 Hz), 1.25 (overlapping d, 3H, J = 5.9 Hz); \textsuperscript{13}C NMR δ 182.0 (+), 165.1 (+), 149.2 (+), 139.3 (+), 133.6 (+), 132.3 (-), 130.4 (-), 128.5 (-), 126.9 (-), 126.8 (-), 116.0 (-), 110.0 (-), 105.9 (+), 89.0 (+), 85.8 (+), 78.8 (+), 78.2 (-), 74.2 (-), 47.2 (+), 22.7 (-), 22.6 (-), 22.5 (-), 22.4 (-); IR (neat) 3383, 3207, 2976, 2215, 1770, 1094 cm\textsuperscript{-1}. 
9-Benzyl-2,3-diisopropoxy-9H-carbazole-1,4-dione (69) and 2,3-diisopropoxy-1H-cyclopenta[b]quinolin-1-one (34a).

4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone (48) (130 mg, 0.32 mmol) was slurried along with CuI (122 mg, 0.64 mmol) in dry DMF (3 mL) and was heated to 100 °C for 3h. The reaction was cooled, diluted with 100 mL Et₂O and filtered through a small pad of Celite. The Celite was also washed with Et₂O (3 X 25 mL). The combined organic layers were washed with 200 mL brine, dried (Na₂SO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 9:1) to afford 69 (16 mg, 0.039 mmol, 12%) as a yellowish oil and 34a (quinoline) (10 mg, 0.034 mmol, 10%). NMR data for 69. ¹H NMR δ 7.5 (d, 1H, J = 6.6 Hz), 7.37 (d, 1H, J = 7.2 Hz), 7.33-7.26 (m, 5H), 6.95 (t, 1H, J = 7.8 Hz), 6.76 (t, 1H, J = 7.2 Hz), 6.00 (d, 1H, J = 7.2 Hz), 5.50 (heptet, 1H, J = 6.6 Hz), 5.44 (heptet, 1H, J = 6.0 Hz), 5.00 (s, 2H), 1.38 (overlapping d, 6H, J = 6.0 Hz), 1.37 (overlapping d, 6H, J = 6.0 Hz); ¹³C NMR δ 186.2 (+), 185.3 (+), 159.7 (+), 155.7 (+), 149.4 (+), 148.2 (+), 136.9 (+), 131.7 (-), 130.5 (+), 128.5 (-), 128.4 (-), 127.5 (-), 124.2 (-), 122.3 (-), 106.6 (-), 105.7 (+), 74.5 (-), 74.4 (-), 54.0 (+), 23.0 (-), 22.9 (-); IR (neat) 2980, 1730, 1667, 1090 cm⁻¹.

4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone (88).

Benzyl-but-3-ynyl-amine⁵⁸ (83) (783 mg, 4.92 mmol) was dissolved in 10 mL of dry THF and subsequently cooled to -40 °C. n-BuLi (2.0M in pentane, 2.50 mL,
5.00 mmol) was added slowly via syringe and stirred for 15 minutes at -40 ºC. A cold (-40 ºC) 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (27) (989 mg, 4.99 mmol) /THF (10 mL) solution was added to the lithiated butyne and stirred for 30 minutes at -40 ºC. The reaction was quenched at -40 ºC with 30 mL water. The resulting mixture was extracted with (3 X 50 mL) diethyl ether. The organic layers were combined, dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, EtOAc) to give 88 (1.489 g, 4.02 mmol, 85%) as a yellow oil. ¹H NMR (270 MHz) δ 7.37 – 7.22 (m, 5H), 4.93 (overlapping heptet, 1H, J = 6.3 Hz), 4.86 (overlapping heptet, 1H, J = 6.3 Hz), 3.79 (s, 2H), 2.76 (t, 2H, J = 6.5 Hz), 2.52 (t, 2H, J = 6.5 Hz), 1.39 (d, 6H, J = 6.3 Hz), 1.29 (dd, 6H, J = 3.94, 5.94 Hz); ¹³C NMR δ 181.8 (+), 165.1 (+), 138.9 (+), 133.1 (+), 128.4 (-), 128.3 (-), 127.1 (-), 86.5 (+), 77.8 (-), 77.4 (+), 77.3 (+), 73.7 (-), 22.7 (-), 22.6 (-), 22.5 (-), 22.4 (-), 19.5 (+); IR (neat) 3293 (br.), 2231, 2060, 2978, 1772, 1623 cm⁻¹.

1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione (91).

4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone (88) (221 mg, 0.618 mmol) was dissolved in 100 mL toluene and heated at reflux for 21 hours. The reaction was cooled to room temperature and the solvent was removed. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc 8:2 then 1:1) to give 91 (113 mg, 0.32 mmol, 51%) as a blue oil. It was noticed that during the column the residue changed in color from a slow moving yellow to faster moving green and then finally to blue. ¹H NMR (270
MHz) δ 7.32 – 7.22 (m, 5H), 5.06 (heptet, 1H, J = 6.2 Hz), 4.88 (s, 2H), 4.47
(heptet, 1H, J = 6.3 Hz), 3.55 (t, 2H, J = 10.6 Hz), 2.80 (t, 2H, J = 10.5 Hz), 1.32
(d, 6H, J = 8.3 Hz), 1.30 (d, 6H, J = 8.3 Hz); 13C NMR (150 MHz) δ 180.3 (+),
177.9 (+), 149.0 (+), 148.6 (+), 136.6 (+), 128.7 (-), 128.5 (-), 127.9 (-), 127.7 (+),
112.9 (+), 76.2 (-), 75.5 (-), 52.4 (+), 51.5 (+), 23.9 (+), 22.8 (-), 22.5 (-); IR (neat)
2975, 1760, 1617 cm⁻¹.

5,6-Diisopropoxy-2,3-dihydro-1H-indole-4,7-dione (93).

1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione (91) (77 mg, 0.216
mmol) was dissolved in 10 mL methanol. Ammonium formate pentahydrate (366
mg, 2.16 mmol) and a portion of 10% Pd/C (43 mg) were added to the flask and
the reaction was heated to reflux for 2 hours. The opaque dark blue solution
turned clear light blue in color after about 5 minutes into the heating. The
reaction was allowed to cool to room temperature and filtered through a small
pad of Celite with excess methanol. The methanol was removed and the residue
was diluted with 100 mL CH₂Cl₂ and washed with 50 mL of water. The organic
layer was dried (Na₂SO₄), filtered and concentrated. The residue was
chromatographed on silica gel (hexanes:EtOAc 1:1) yielding 93 (16 mg, 0.060
mmol, 28%) as a green-blue oil. 1H NMR δ 4.99 (heptet, 1H, J = 6.0 Hz), 4.89
(br. s, 1H), 4.48 (heptet, 1H, J = 6.9 Hz), 3.71 (t, 2H, J = 10.2 Hz), 2.93 (t, 2H, J =
10.2 Hz), 1.30 (d, 6H, J = 6.0 Hz), 1.26 (d, 6H, J = 6.0 Hz); 13C NMR δ 197.6 (+),
197.5 (+), 179.0 (+), 178.8 (+), 173.6 (+), 151.8 (+), 149.7 (+), 141.9 (+), 112.3
(+), 76.4 (-), 75.5 (-), 46.8 (+), 26.5 (+), 22.8 (-), 22.5 (-); IR (neat) 3344 (br.), 2977, 1664 cm⁻¹.

**1-Benzyl-5,6-diisopropoxy-1H-indole-4,7-dione (94).**

1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione (91) (40 mg, 0.113 mmol) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (27 mg, 0.117 mmol) was dissolved in 5 mL benzene. The reaction was allowed to stir at room temperature for 22 hours and then was heated to reflux for 24 additional hours. The solvent was removed and the residue was chromatographed (SiO₂, hexanes:EtOAc 8:2) yielding 94 (26 mg, 0.073 mmol, 65%) as a orange oil. ¹H NMR ‰ 7.34-7.24 (m, 5H), 6.84 (d, 1H, J = 2.4 Hz), 6.56 (d, 1H, J = 3.0 Hz), 5.53 (s, 2H), 4.78 (heptet, 1H, J = 6.0 Hz), 7.73 (heptet, 1H, J = 6.0 Hz), 1.32 (d, 6H, J = 6.6 Hz), 1.31 (d, 6H, J = 6.0 Hz); ¹³C NMR ‰ 180.1 (+), 175.6 (+), 146.9 (+), 146.7 (+), 136.2 (+), 129.6 (-), 128.9 (-), 128.2 (-), 127.7 (-), 127.6 (+), 125.7 (+), 107.7 (-), 76.1 (-), 52.0 (+), 22.7 (-), 22.6 (-); IR (neat) 3112, 2976, 1648 cm⁻¹.

**tert-butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate (89).** tert-butyl benzylbut-3-ynylcarbamate⁵⁷ (87) (641 mg, 2.47 mmol) was dissolved in 5 mL THF and cooled to -78 °C. The n-BuLi (2.0M in hexanes, 1.25 mL, 2.50 mmol) was added over a 15 min. period and allowed to stir for 30 minutes. 27 was added (5 mL) THF was added via cannula and allowed to stir for 30 minutes. The reaction was quenched with 30 mL and extracted with 3X 50 mL Et₂O, dried (MgSO₄), filtered and concentrated. The
residue was chromatographed on silica gel (hexanes:EtOAc 8:2) yielding 89 as a thick yellow oil (704 mg, 1.54 mmol, 62%). $^1$H NMR $\delta$ (270 MHz) 7.31-7.16 (m, 5H), 4.97 (heptet, 1H, $J = 6.2$ Hz), 4.84 (heptet, 1H, $J = 6.2$ Hz), 4.51 (s, 2H), 4.30 (br. d, 1H, $J = 11.1$ Hz), 3.38 (br. s, 1H), 3.26 (br. s, 1H), 2.45 (br. s, 2H), 1.41 (s overlapping with d at 1.40, 9H), 1.40 (d overlapping with s at 1.41, 6H, $J = 6.3$ Hz), 1.26 (d, 6H, $J = 5.2$ Hz). $^{13}$C NMR $\delta$ (67.5 MHz) 181.1 (+), 164.9 (+), 155.3 (+), 138.1 (+), 137.9 (+), 133.3 (+), 128.2 (-), 127.6 (-), 126.9 (-), 86.9 (+), 86.2 (+), 79.9 (-), 78.2 (-), 77.5 (-), 77.4 (+), 76.2 (-), 73.6 (+), 51.2 (-), 50.3 (-), 45.4 (-), 45.1 (-), 30.7 (+), 28.2 (+), 22.5 (+), 22.4 (+), 22.3 (+), 18.7 (-), 18.5 (-). IR (neat) 3340 br., 2990, 2930, 2106, 1767, 1686, 1094 cm$^{-1}$.

**tert-butyl benzyl-2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethylcarbamate (92).** tert-butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate (89) (560 mg, 1.22 mmol) was dissolved in 20 mL 1,2-DCE and placed in a thick walled flask. The flask was sealed and heated to 100 °C for 22h. The reaction was cooled to room temperature and solvents were removed. The resulting residue was chromatographed on silica gel (hexanes:EtOAc; 8:2) yielding 92 as an orange oil (266 mg, 0.58 mmol, 48%) $^1$H NMR (270 MHz) $\delta$ 7.40-7.23 (m, 5H), 6.26 (s, 1H), 4.79 (heptet, 2H, $J = 5.8$ Hz), 4.45, (s, 2H), 3.40 (br. s, 2H), 2.54 (t, 2H, $J = 6.7$ Hz), 1.43-1.27 (m, 21H). $^{13}$C NMR $\delta$ 184. 3 (+), 155.6 (+), 145.3 (+), 131.3 (+), 128.5 (+), 128.3 (-), 128.1 (-), 127.3 (-), 80.0 (+), 76.0 (+), 75.9 (+), 50.8 (+), 45.5 (+), 28.6 (-), 28.3 (-), 28.1 (-), 22.9 (), 22.7 (-), 22.6 (-). IR (neat) 2977, 2933, 1686, 1654, 1095 cm$^{-1}$.
1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione (91). tert-butyl benzyl2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethylcarbamate (92) (200 mg, 0.44 mmol) was dissolved in CH₂Cl₂ (20 mL) and treated with 1.5 mL trifluoroacetic acid³ at 0 °C for 3 h. The reaction was then warmed to 50 °C for 1 h. The reaction was cooled to room temperature and the solvents were removed under reduced pressure. The resulting residue was neutralized with 30 mL aqueous saturated NaHCO₃ and extracted with 3X 30 mL portions of CH₂Cl₂. The organic layer was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to give 91 (80 mg, 0.22 mmol, 51%) as a blue oil.

[2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (33a). A solution of 28a (184 mg, 0.44 mmol) in N,N-dimethylformamide (DMF) (3 mL) was heated to 100 °C for 6 h. The reaction was cooled to ambient temperature, diluted with 100 mL Et₂O and filtered through a pad of Celite and rinsed with 2X 25 mL Et₂O. The organic washings were combined and washed with 20 mL brine, dried (Na₂SO₄) and concentrated. The solvent was then removed under reduced pressure and the residue was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to give 33a (19 mg, 0.048 mmol, 11%) as an orange solid. mp 93-96 °C; ¹H NMR (270 MHz) δ 7.91 (dd, 1H, J=7.9 and 1.6 Hz), 7.80 (d, 1H, J=8.1 Hz), 7.44 (s, 1H),
overlapping 7.40 (t, 1H, J=8.7 Hz), 7.13 (t, 1H, J=7.5 Hz), 6.54 (br s, 1H), 5.59 (m, 2H), 1.51 (s, 9H), 1.40 (d, 6H, J=6.3 Hz), 1.37 (d, 6H, J=6.1 Hz).

This reaction was also repeated in several different temperatures and times and are summarized in Table 5.

**Table 5: Copper Mediated Reaction Conditions for 28a**

<table>
<thead>
<tr>
<th>Temp/Time/28a</th>
<th>Cul</th>
<th>33a</th>
<th>Recovered 28a</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 °C, 24h, 28a 120 mg, 0.29 mmol</td>
<td>Yes 2 eq</td>
<td>No Reaction</td>
<td>Not Calculated</td>
</tr>
<tr>
<td>85 °C, 24h, 28a (120 mg, 0.29 mmol)</td>
<td>Yes 2 eq</td>
<td>10 mg, 0.024 mmol, 8%</td>
<td>29 mg, 0.069 mmol, 24%</td>
</tr>
<tr>
<td>100 °C, 6h, 28a 184 mg, 0.44 mmol</td>
<td>Yes 2 eq</td>
<td>19 mg, 0.048 mmol, 11%</td>
<td>Not recovered</td>
</tr>
<tr>
<td>120 °C, 1h, 28a 212 mg, 0.51 mmol</td>
<td>Yes 2 eq</td>
<td>24 mg, 0.057 mmol, 11%</td>
<td>70 mg, 0.17 mmol, 32%</td>
</tr>
<tr>
<td>120 °C, 1h, 28a 166 mg, 0.40 mmol</td>
<td>No</td>
<td>38 mg, 0.091 mmol, 23%</td>
<td>13 mg, 0.032 mmol, 8%</td>
</tr>
</tbody>
</table>

4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone (51a). 4-Ethynyl-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone\textsuperscript{69} 39 (370 mg, 1.65 mmol), bis(triphenylphosphine)palladium dichloride (56 mg, 0.080 mmol), copper iodide (317 mg, 1.66 mmol) were slurried in 30 mL NEt\textsubscript{3}. Iodonitrobenzene (418 mg, 1.68 mmol) was added after five minutes and the reaction was allowed to stir. After 24 hours the reaction was diluted with 50 mL water and extracted with diethyl ether (3 x 50 mL). The combined organic layers
were washed with 20 mL 10% NH4OH, dried (MgSO4), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO2, hexanes: EtOAc, 1:1) to give 51a (300 mg, 0.57 mmol, 53%) as a yellow oil. 1H NMR (270 MHz) δ 8.07 (dd, 1H, J = 1.8, 8.3 Hz), 7.66 (dd, 1H, J = 1.8, 7.9 Hz), 7.59 (dt, 1H, J = 1.1, 7.5 Hz), 7.49 (dt, 1H, J = 1.6, 8.1 Hz), 5.06 (heptet, 1H, J = 6.1 Hz), 4.91 (heptet, 1H, J = 6.1 Hz), 3.03 (br. s, 1H), 1.47 (d, 6H, J = 6.1 Hz), 1.34-1.31 (overlapping d, 6H, J = 6.2, 6.1 Hz). 13C NMR (67.5 MHz) δ 179.6 (+), 163.9 (+), 149.4 (+), 135.0 (-), 134.2 (+), 132.9 (-), 129.3 (-), 124.6 (-), 117.3 (+), 91.3 (+), 83.7 (+), 79.1 (+), 78.4 (-), 74.3 (-), 22.6 (-), 22.5 (-). IR (neat) 3348 br., 2980, 2934, 2368, 1774, 1609, 1319 cm⁻¹.

2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione (51d) and 2,3-diisopropoxy-5-(2-nitrophenyl)cyclohexa-2,5-diene-1,4-dione (51c). 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone 51a was dissolved in 200 mL toluene and heated to reflux for 5 hours. The reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was chromatographed (SiO2, hexanes:EtOAc, 8:2) yielding 51c (141 mg, 0.41 mmol, 33%) as a brown oil and 51d (47 mg, 0.14 mmol, 11%). Data for 51c 1H NMR δ 8.15 (dd, 1H, J = 1.2, 8.4 Hz), 7.70 (s, 1H), 7.68 (dd, 1H, J = 1.2, 7.2 Hz), 7.64 (dt, 1H, J = 1.2, 7.2 Hz), 7.56 (dt, 1H, J = 1.2, 6.0 Hz), 5.64 (heptet, 1H, J = 6.0 Hz), 4.95 (heptet, 1H, J = 6.0 Hz), 1.41 (d, 6H, J = 6.0 Hz), 1.35 (d, 6H, J = 6.0 Hz). 13C NMR δ 184.7 (+), 183.8 (+), 152.5 (+), 150.7 (+), 148.1 (+), 132.8 (-), 132.5 (-), 131.2 (-), 130.2 (+), 129.1 (+), 128.3 (+),
124.6 (-), 75.2 (-), 75.1 (-), 23.1 (-), 22.9 (-). IR (neat) 2990, 1732, 1673, 1655, 1340 cm\(^{-1}\). Data for 51d \(^1\)H NMR δ 7.72-7.58 (br. d, 2H), 7.24 (d overlapping CHCl\(_3\), 1H), 7.10 (t, 1H, J = 7.3 Hz), 6.47 (s, 1H), 5.51 (overlapping heptets, 2H, J = 6.1), 1.41 (d overlapping d at 1.38, 6H, J = 7.1 Hz), 1.38 (d overlapping d at 1.41, 6H, J = 6.5 Hz)
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6 Skraup, Z, H. Ber. 1880, 13, 2086
9 Knorr, L. Ber., 1883, 16, 2593
11 Conrad, M.; Limpach, L. Ber., 1887, 20, 944.


38 Söderberg, B. C. G., Dantale, S. W. (unpublished results)
48 Söderberg, B. C. G., Dantale, S. W. (unpublished results)


70 Switched to 1,2-dichloro based on: Söderberg, B. C. G., Dantale, S. W. (unpublished results)


Appendix
Figure 4: $^1$H Spectrum of (4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester 37b
Figure 5: $^{13}$C Spectrum of (4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester 37b
Figure 6: $^1$H Spectrum of (2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester 37c
Figure 7: $^{13}$C Spectrum of (2-iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester 37c
Figure 8: $^1$H Spectrum of (2-iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 37d
Figure 9: $^{13}$C Spectrum of (2-iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 37d
Figure 10: $^1$H Spectrum of (4-Chloro-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester 38b
Figure 11: $^{13}$C Spectrum of (4-Chloro-2-(trimethylsilylethylnyl)phenyl)-carbamic acid 1,1-dimethylethyl ester 38b
Figure 12: $^1$H Spectrum of (5-Methoxy-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 38c
Figure 13: $^{13}$C Spectrum of (5-Methoxy-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 38c
Figure 14: $^1$H Spectrum of (5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 38d
Figure 15: $^{13}$C Spectrum of (5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 38d
Figure 16: $^1$H Spectrum of (4-trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 38e
Figure 17: $^{13}$C Spectrum of (4-trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 38e
Figure 18: $^1$H Spectrum of (4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 26b
Figure 19: $^{13}$C Spectrum of (4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 26b
Figure 20: $^1$H Spectrum of (2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester 26c
Figure 21: $^{13}$C Spectrum of (2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethyethyl ester 26c
Figure 22: $^1$H Spectrum of (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 26d
Figure 23: $^{13}$C Spectrum of (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 26d
Figure 24: $^1$H Spectrum of (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 26e
Figure 25: $^{13}$C Spectrum of (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 26e
Figure 26: $^1$H Spectrum of [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethylnyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28a
Figure 27: $^{13}$C Spectrum of [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28a
Figure 28: $^1$H Spectrum of [4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28b
Figure 29: $^{13}$C Spectrum of [4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28b
Figure 30: $^1$H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester 28c and butyl addition product of diisopropyl squarate
Figure 31: $^{13}$C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester 28c and butyl addition product of diisopropyl squarate
Figure 32: $^1$H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester 28c
Figure 33: $^{13}$C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester 28c
Figure 34: $^1$H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester 28d
Figure 35: $^{13}$C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enzyme)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester 28d
Figure 36: $^1$H Spectrum of [4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester 28e
Figure 37: $^{13}$C Spectrum of [4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester 28e
Figure 38: $^1$H Spectrum of [2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 33a
Figure 39: $^{13}$C Spectrum of [2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 33a
Figure 40: $^1$H Spectrum of [4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 33b
Figure 41: $^{13}$C Spectrum of [4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 33b
Figure 42: $^1$H Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxy-phenyl]-carbamic acid 1,1-dimethylethyl ester 33c
Figure 43. $^{13}$C Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxy-phenyl]-carbamic acid 1,1-dimethylethyl ester 33c
Figure 44: $^1$H Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester 33d
Figure 45: $^{13}$C Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester 33d
Figure 46: $^1$H Spectrum of [4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyridinyl]-carbamic acid 1,1-dimethylethyl ester 33e
Figure 47: $^{13}$C Spectrum of [4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyridinyl]-carbamic acid 1,1-dimethylethyl ester 33e
Figure 48: $^1$H Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-one 34a
Figure 49: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-one 34a
Figure 50: $^1$H Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-one 34b
Figure 51: $^{13}$C Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-one 34b
Figure 52: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-one 34c
Figure 53: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-one 34c
Figure 54: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-one 34d
Figure 55: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-one 34d
Figure 56: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-aza-cyclopenta[b]quinolin-1-one 34e
Figure 57: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-aza-cyclopenta[b]quinolin-1-one 34e
Figure 58: $^1$H Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35a
Figure 59: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)cyclo-penta[b]quinolin-1-ol 35a
Figure 60: $^1$H Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35b
Figure 61: $^{13}$C Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35b
**Figure 62**: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-ol 35c
Figure 63: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-ol 35c
Figure 64: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-ol 35d
Figure 65: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-ol 35d
Figure 66: $^1$H Spectrum of 2,3-Di(1-methylethoxy)-6-azacyclopenta[b]quinolin-1-ol 35e
Figure 67: $^{13}$C Spectrum of 2,3-Di(1-methylethoxy)-6-azacyclopenta[b]quinolin-1-ol 35e
Figure 68: $^1$H Spectrum of [2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethylethyl ester 41
Figure 69: $^{13}$C Spectrum of [2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethylethyl ester 41
Figure 70: $^1$H Spectrum of E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 42
Figure 71: $^{13}\text{C}$ Spectrum of E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 42
Figure 72: $^1$H Spectrum of 2-(1-Methylethoxy)-3-methylcyclopenta[b]quinolin-1-one 43
Figure 73: $^{13}$C Spectrum of 2-(1-Methylethoxy)-3-methylcyclopenta[b]quinolin-1-one 43
Figure 74: $^1$H Spectrum of 2-(1-methylethoxy)-3-methylcyclopenta[b]quinolin-1-ol 44
Figure 75: $^{13}$C Spectrum of 2-(1-methylethoxy)-3-methylcyclopenta[b]quinolin-1-ol 44
Figure 76: $^1$H Spectrum of N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide. 46
Figure 77: $^{13}$C Spectrum of N-[2-(1-Hydroxy-2,3-diisoproxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide 46
Figure 78: $^1$H Spectrum of N-[2-(3,4-Diisopropoxy-2,5-dioxo-cyclopent-3-enylidenemethyl)-phenyl]-acetamide 51
**Figure 79**: $^{13}$C Spectrum of N-[2-(3,4-Diisopropoxy-2,5-dioxo-cyclopent-3-enylidenemethyl)-phenyl]-acetamide 51
Figure 80: $^1$H Spectrum of 3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. 70
Figure 81: $^{13}$C Spectrum of 3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. 70
Figure 82: $^1$H Spectrum of N-[2-(2-isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide 71
Figure 83: $^{13}$C Spectrum of N-[2-(2-Isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide 71
Figure 84: $^1$H Spectrum of tert-butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)ethynyl)phenylcarbamate 72
Figure 85: $^{13}$C Spectrum of tert-butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)ethynyl)phenylcarbamate 72
Figure 86: $^1$H Spectrum of 4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 48
Figure 87: $^{13}$C Spectrum of 4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 48
Figure 88: $^1$H Spectrum of 9-Benzyl-2,3-diisopropoxy-9H-carbazole-1,4-dione 69
Figure 89: $^{13}$C Spectrum of 9-Benzyl-2,3-diisopropoxy-9H-carbazole-1,4-dione
Figure 90: $^1$H Spectrum of 4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-disopropoxy-cyclobut-2-enone 88
Figure 91: $^{13}$C Spectrum of 4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 88
Figure 92: $^1$H Spectrum of 1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione 91
Figure 93: $^{13}$C Spectrum of 1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione 91
Figure 94: $^1$H Spectrum of 5,6-Diisopropoxy-2,3-dihydro-1H-indole-4,7-dione 93
Figure 95: $^{13}$C Spectrum of 5,6-Diisopropoxy-2,3-dihydro-1H-indole-4,7-dione 93
Figure 96: $^1$H Spectrum of 1-Benzyl-5,6-diisopropoxy-$1H$-indole-4,7-dione 94
Figure 97: $^{13}$C Spectrum of 1-Benzyl-5,6-diisopropoxy-1H-indole-4,7-dione 94
Figure 98: $^1$H Spectrum of tert-buty benzyl-4-(1-hydroxy-2,3-diisoproxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate 89
Figure 99: $^{13}$C Spectrum of tert-butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate 89
Figure 100: $^1$H Spectrum of tert-butyl benzyl-2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethylcarbamate 92
Figure 101: $^{13}$C Spectrum of $\text{tert}$-butyl benzyl-2-($\text{4,5}$-diisopropoxy-$\text{3,6}$-dioxocyclohexa-$\text{1,4}$-diene$\text{yl})$ethylcarbamate 92
Figure 102: $^1$H Spectrum of 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone 51a
Figure 103: $^{13}$C Spectrum of 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone 51a
Figure 104: $^1$H Spectrum of 2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione 51d
Figure 105: $^{13}$C Spectrum of 2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione 51d
Figure 106: $^1$H Spectrum of 2,3-diisopropoxy-5-(2-nitrophenyl)cyclohexa-2,5-diene-1,4-dione 51c
Figure 107: Expanded view of gHMBC Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-ol 35a
Figure 108: Expanded view of gHMOC Spectrum of 2,3-Di(1-methylethoxy)cyclopenta\([b]\)quinolin-1-ol 35a